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Original Communications

NUTRITION STUDY IN PREGNANCY*

CORRELATION BETWEEN DIETARY SURVEY OF VITAMIN A CONTENT AND DARK ADAPTATION TIME

PHILIP F. WILLIAMS, M.D., BERNARD HARK, M.D., AND
FLORENCE G. FRALIN, B.S., PHILADELPHIA, PA.
(From the Prenatal Clinics of the Presbyterian and Jewish Hospitals)

THIS report presents the results of an estimation of the vitamin A content in the diets of 123 pregnant women, a determination of their dark adaptation time by the adaptometer, a study of the effect upon the deficiencies following administration of vitamin A concentrate, and a correlation of the findings with several obstetric factors.

Vitamin A, an essential food factor, is metabolized in the human body from its precursors, which, in turn, are metabolic products of plants. It is one of an increasing group of organic substances regarded as indispensable for growth and maintenance of normal structure and function of body tissue. It is said to be intimately concerned with the reproductive processes of experimental and domestic animals. This vitamin in its most nearly pure naturally occurring form is found in fish liver oils. In the human body, carotene, its precursor or provitamin, is converted to vitamin A in the liver. Carotene is contained in the yellow or green colored matter of many vegetables and fruits.

Eggs, milk, and some milk products, and liver are the most important vitamin A food sources of animal origin. The best plant sources are the green or yellow fruits and vegetables.

*This study was made under a grant from the Selina B. McIlhenny Fund for Clinical Investigation in the Presbyterian Hospital in Philadelphia.

Read by invitation at the Third Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists at Richmond, Virginia, February 9, 1940.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

The vitamin A activity of milk and eggs is derived from the plant material consumed by the cow and the hen; and milk becomes a very important source of vitamin A supply when one considers that it is consumed in fairly large quantities.

Animal liver contains a high concentration of vitamin A (approximately 2,780 Sherman units per ounce of beef liver); it is the site of transformation of carotene into actual vitamin A, and surplus vitamin A is stored there. But, "increased appreciation of, and consumer demand for, liver cannot be met by increased production of liver as an independent food crop."*

Thin green leaves are among the best sources of vitamin A. There seems to be a parallel between chlorophyll content and vitamin A activity, but the exact relationship has not yet been established. The yellow color of the carotene may be an index of the vitamin A activity in many plant products, as for example, carrots and sweet potatoes, two valuable vegetable sources, and apricots, yellow peaches and bananas, very good fruit sources.[1]

Vitamin A is essential to normal nutrition at all ages. One of the early symptoms of deficiency is hemeralopia, poor visual adaptation to semidarkness. Mild deficiency symptoms reported include retarded growth, possible lowered resistance to infection, particularly in the upper respiratory tract, lack of vigor and appetite, decreased reproduction and lactation, dry skin and poor teeth. More serious deficiencies reported include such symptoms as xerophthalmia, lowered resistance to infections entering mucous surfaces, sterility, loss of weight, calculus formation in kidney and bladder, and a weakening and metaplasia of epithelial tissues.

The requirements for the human being have been worked out from various aspects and are usually expressed in terms of international units per kilogram of body weight. Quantitatively, according to Guilbert and Hart,[2] the requirement for vitamin A is strikingly small; six to eight micrograms daily per kilogram of body weight are necessary for cattle, sheep, and swine.

Since the symptom of partial night blindness lends itself to physical measurement, several investigators have made observations on the amounts of vitamin A necessary to prevent it. They based their conclusions on the ability of their subjects to discern differences in brightness of illumination.

After studying two matched groups of young male adults, Edmund and Clemmesen[3] concluded that 20 to 22 international units of vitamin A value per kilogram of body weight should prevent visual dysadaptation. An average of 40 international units per kilogram maintained an optimal visual response without providing body storage in the series studied by Booher, Collison, and Hewston.[4]

Stiebeling and Phipard[5] conclude from the Booher study that the average American diet should provide an average of 60 international units per kilogram to cover average minimum requirements for maintaining optimal visual response. They suggest that to obtain a storage reserve and to provide for the needs of those with higher requirements it would appear practicable to establish a 50 per cent margin

*Sherman: *Chemistry of Foods and Nutrition*, New York, 1937, The Macmillan Company.

of safety as an aim in ideal dietary plans. For a 70 kilogram man this would amount to at least 6,000 international units of vitamin A value per day. Six to eight thousand units of vitamin A value can be furnished by ordinary food if great care is taken in its selection.

Several observers[6-8] have noted that only minute traces of vitamin A and carotene are found in the serum of blood from the umbilical cord of human infants. Others have noted that the fetal liver contains only 14 to 17 units per gram as against an average content in the adult liver of 220 units per gram. Dann[9] found that in spite of the apparent necessity of vitamin A for fetal growth it was impossible to raise the vitamin content of the livers of fetal rats by administering either vitamin A or carotene in large doses to the pregnant mothers. By administering enormous doses of vitamin A to the pregnant rabbit, a slight relative increase in the storage of vitamin A in the fetal liver was accomplished. The deleterious effects upon the reproductive process in dairy animals, swine, and experimental animals of a diet deficient in vitamin A values have been established.

Sure[10] and Mason[11] have shown that a lack of vitamin A in the diets of rats upset the estrous cycle, and caused resorption of the fetus; if a litter was born, the young were immature and showed signs of incipient xerophthalmia. Cattle in California, deprived of green food during a dry season, had stillborn calves whose livers showed no vitamin A. Those calves born alive succumbed readily to infections. Here estrus also failed to return.[12]

These effects of a vitamin A deficiency accentuate the importance for an optimum amount of this food factor in the diet during pregnancy. Among other basic reasons for such an increase may be mentioned the increased metabolism of the pregnant woman, the very active metabolic processes of the fetus in relation to its weight, and the need for an increased storage in the woman's body to provide for the demands of lactation. The surprising difference between content of vitamin A in the fetal liver and the adult liver, and the fact that but minute traces of either vitamin A or carotene are found in the umbilical cord blood serum suggest that the placenta prevents the passage of any marked quantity of vitamin A to the fetus and its structures. This is in contrast to the finding of an increased amount of vitamin C in the cord blood of the fetus as compared with a simultaneous maternal blood content. To us the question is not answered as to the reason for such a small amount of such an essential growth factor as vitamin A in the fetal blood and the tissues. If the fetus has the same comparative need for vitamin A in its metabolic oxidative processes, in what form is it transmitted from the mother?

The newborn child requires 2,000 units of vitamin A a day[13] for its growth and for the liver storage which increases rapidly in the early weeks of life. Such need increases with the growth of the child. This necessitates a maternal storage during pregnancy as well as a continuance of optimum requirements during lactation.

The argument that excess storage does take place during pregnancy can be somewhat strengthened by the discovery in the literature that maternal storage is more than double that of ordinary human storage.

Busson[14] analyzed for vitamin A the liver of one woman who died in shock shortly after cesarean section, and has reported the determination of 462 Lovibond Blue Units in 0.5 Gm. of liver. Although its validity might be questioned, applying Moore's[15] conversion formula, 1 B.U. $\times$ 0.6 $=$ 1 international unit, the liver of this patient contained 544.4 international units of vitamin A per gram, as contrasted with 220 international units per gram of normal human adult liver.

The increased requirements of pregnancy and lactation probably are met by doubling the adult's usual requirements per unit of body weight. For a 132 pound, 60 kilogram, pregnant woman, then, at double the usual 60 unit value for minimum requirement, the daily requirement would be 7,200 international units of vitamin A value. The Technical Commission of the League of Nations[16] recommends 9,000 international units of vitamin A for the pregnant and lactating woman.

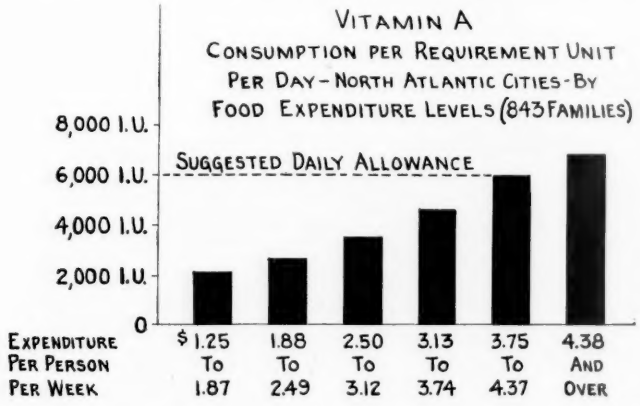

Fig. 1.—Vitamin A consumption per requirement unit per day, North Atlantic cities, by food expenditure levels (843 families). (From Stiebeling and Phipard.[5])

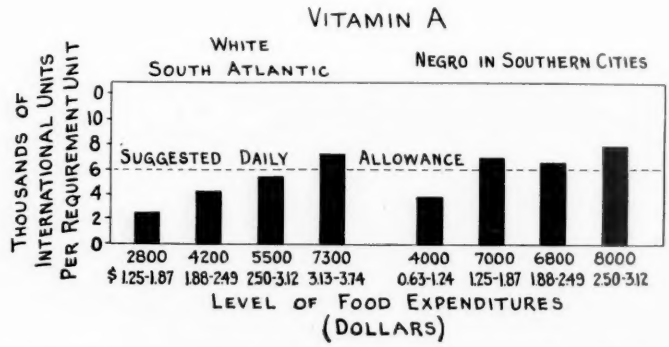

Fig. 2.—Vitamin A consumption per requirement unit per day. White in South Atlantic cities and Negro in Southern cities, by food expenditure levels. (Adapted from Stiebeling and Phipard.)

Dr. Maurice B. Strauss in a personal communication says, "I feel that it is wise to hold out for high levels, particularly in view of the many metabolic and gastrointestinal changes which occur in pregnancy and which probably alter the absorption, utilization and requirement of nutritional factors."

In their recent estimate of the adequacy of diets of different population groups, Stiebeling and Phipard investigated, among other food factors, the content of vitamin A. They found that values as high as their suggested daily allowance scale for the requirement unit of an adult male, twenty years or over, of 6,000 international units were obtained in groups of families living in Southern cities, even when their expenditures for food were as little as $0.63 to $1.24 a person per week. In their dietary survey of the families of employed workers in eight major geographical centers of the United States, the authors brought to light many surpris-

ing facts regarding the distribution of dietary vitamin A values. It is of interest at this meeting to compare the North Atlantic cities, which include Philadelphia, the South Atlantic cities, and the negro of the Southern cities, for the average values for vitamin A in their diets at various economic levels.

In the North Atlantic cities, according to Stiebeling and Phipard (Fig. 1), at a food expenditure level of $1.25 to $1.87 a person a week, the average vitamin A value of the diets of the families investigated was 2,100 international units a requirement unit a day. Almost 70 per cent of the diets furnished less than 2,000 units, whereas the top 13 per cent furnished more than 4,000 units per requirement unit a day. Even when the expenditure reached $2.50 to $3.12 a person a week, as many as 29 per cent of the families in the North Atlantic cities obtained fewer than 2,000 units a requirement unit a day. In the South Atlantic cities with an expenditure of $1.25 to $1.87 (Fig. 2), the average value reached 2,800 units, a 25 per cent increase over the North Atlantic area. At the same financial output, the negro in the Southern cities obtained 6,600 units. At $3.13 to $3.74 per person per week for food the South Atlantic average of 7,300 units goes over the required allowance for the first time. The North Atlantic average still trails at 4,200 units, and only approximates the requirement allowance, with 5,900 units, at an expenditure of $3.75 to $4.37 per person per week for food.

Although the cost is unknown it may be interesting at this point to mention the pellagra-producing diet published by Ross and his coworkers[17] in their investigation of the relation of dietary factors to pregnancy toxemia (Table I). It is to be presumed, from the context of their report, that many pregnant women in the South subsist on a diet similar to one which the values show is markedly deficient in vitamin A.

TABLE I. VITAMIN A VALUE IN A PELLAGRA-PRODUCING DIET
(AS REPORTED BY ROSS)

FOOD	QUANTITY (GM.)	VITAMIN A VALUE INT. UNITS
Cornmeal (yellow)	92	770
Cane syrup	105	0
Flour	111	0
Lard	81	0
Rice	25	0
Field peas	90	500-3,000*
Hominy grits	51	0
Fat salt pork	60	300
Total value		1,570-4,070

*Values by different assays.

Consequently, it is evident that in both the North and South Atlantic cities, though to a greater extent in the former, present-day diets go below normal requirements for vitamin A values, even though the money outlay for such a diet is relatively high. And it is to be presumed that the negro of the Southern cities has made a choice of better value and of probably relatively less expense in his selection of sweet potatoes and other cheaper, but more abundant carotene-containing plant products. Where the North Atlantic family buys only four pounds of sweet potatoes to 153 pounds of potatoes, the Southern negro buys in the ratio of 42 to 49: and his consumption of leafy green and yellow vegetables is to that of the white adult of the North Atlantic as 90 is to 75.

With vitamin A and other recognized deficiencies of the diets of the North Atlantic area in mind, we began last year to make a nutrition survey of a series of pregnant women in Philadelphia. There was no selection of the patients, who were attending prenatal clinics at the Presbyterian Hospital and at the Jewish Hospital. Women in all stages of pregnancy and degree of parity, at no particular season of the year were included. A nutritionist interviewed the women personally, instructing them how to record properly their food intake over a period of seven days. When the food records* were returned, all items were

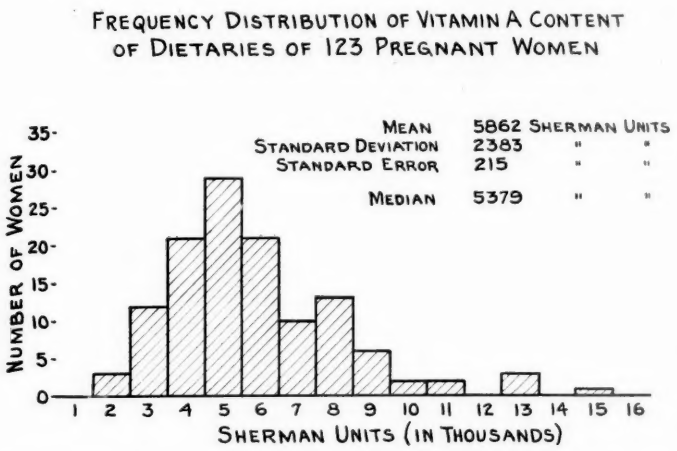

Fig. 3.—Frequency distribution of vitamin A content of dietaries of 123 pregnant women.

scrutinized and checked by the nutritionist during a second personal interview. Although some food records had to be discarded because they were incomplete or inaccurate, we feel that, obtained in the manner described, they furnish a reasonably good picture of the usual diet of these pregnant women.

The food records were then analyzed for their vitamin A values in Sherman units, as set forth in *Food Values of Portions Commonly Served,* First Edition, 1937, prepared by Bowes and Church.[18] All the analyses in this report were computed in Sherman units, because data for average vitamin A values in the international units were not sufficiently complete or definite for our purposes. No conversion into international units was attempted because, as Munsell states, ". . . the derivation of a conversion factor is not a valid procedure. Any implied relationship must be considered as merely indicative."

The vitamin A intake in Sherman units is graphically shown in Fig. 3.

Inasmuch as the food records were computed in Sherman units, there was a need for vitamin requirements in pregnancy also expressed in Sherman units. The most complete ones found were those announced

*The forms used for the food analyses were patterned after those designed for teaching purposes at the Dental School of the University of Pennsylvania.

by the Philadelphia Child Health Society in October, 1938. They include the following standards:

Vitamin A	6,000-	10,000	Sherman units
Vitamin B	900-	1,200	Sherman units
Vitamin C	100-	200	Sherman units
Vitamin G	600-	800	Sherman-Bourquin units
Vitamin D	800		International units

An analysis shows that 62 per cent of the vitamin A values of the food records studied were below the requirements for pregnancy as stated above.

The next step was to measure dark adaptation timing by means of an adaptometer and the test was performed as follows:

The patient was placed in a dark room and exposed for a measured time (three minutes) to a strong bleaching light of controlled intensity. During the exposure period, it was necessary to observe the patient's eyes to see that they were kept open. After the exposure light was extinguished, the patient touched a small knob on the instrument casing and fixed in darkness at that point. This is called tactile sense fixation. The fixation point was so located that the image of the test light fell upon a predominantly rod retinal area (about 20 degrees off the fovea).

Readings for the regeneration of the visual purple were made at given time intervals by increasing the intensity of the test light until it became just barely visible. The patient had not only to report when she saw the test light, but also the direction of its oblong form. This direction could be adjusted by the operator, and thus the veracity of the patient's report was checked.

The earliest manifestation of avitaminosis A is night blindness. It is now known that the ability to see in dim illumination is due to the visual purple, which is regenerated normally only when an adequate supply of vitamin A or its precursor is present. The physiology and pathology of avitaminosis A and dark adaptation have been discussed by Hecht[19] and the diagnosis of latent avitaminosis A with the photometer has been described recently by Feldman.[20] A full discussion will be found in their contributions.

Ricketts[21] tested 40 pregnant women with the Jean's biophotometer and found 16 classified as good, 17 fair, 3 poor, and 4 very poor. There was an opportunity to check 19 cases after administration of carotene in oil with obvious improvement. Two of his cases presented vitamin A deficiencies so severe they simulated toxemias of pregnancy. Both responded to vitamin A therapy.

Edmund and Clemmesen,[3] in a study of 50 women with complicated pregnancies admitted to a municipal hospital in Copenhagen, found that about half of them presented "dysadaptation." This term they apply to pathologic or abnormally high light threshold reading. Their cases presented largely hyperemesis and pyelitis as indications for hospitalization.

We made readings in 123 pregnant women, and checked them, and an opthalmoscopic examination was made to disclose any pathologic lesion of the eye. We have considered five minutes or less as normal readings.

The dark adaptation time in the group ranged from two to eleven minutes. The results are expressed graphically in Fig. 4. The analysis shows that 37.5 per cent of these women had an adaptation time delayed beyond the normal of five minutes.

As a result of finding deficient vitamin A values in such a high percentage of the women by both dietary analyses and dark adaptation time, an attempt was made to correlate the findings in the deficient cases (Fig. 5). In the group under study, no definite tendency is dis-

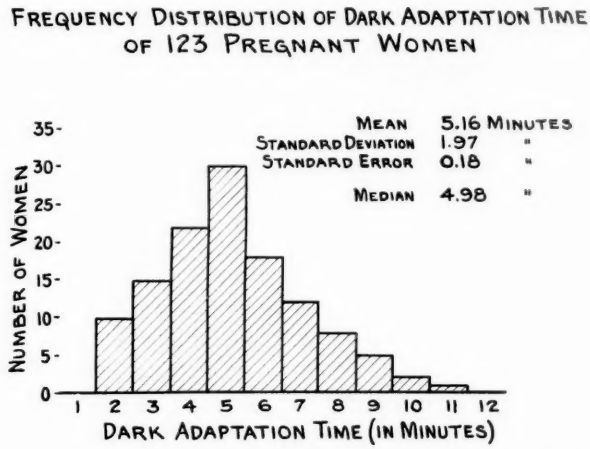

Fig. 4.—Frequency distribution of dark adaptation time of 123 pregnant women.

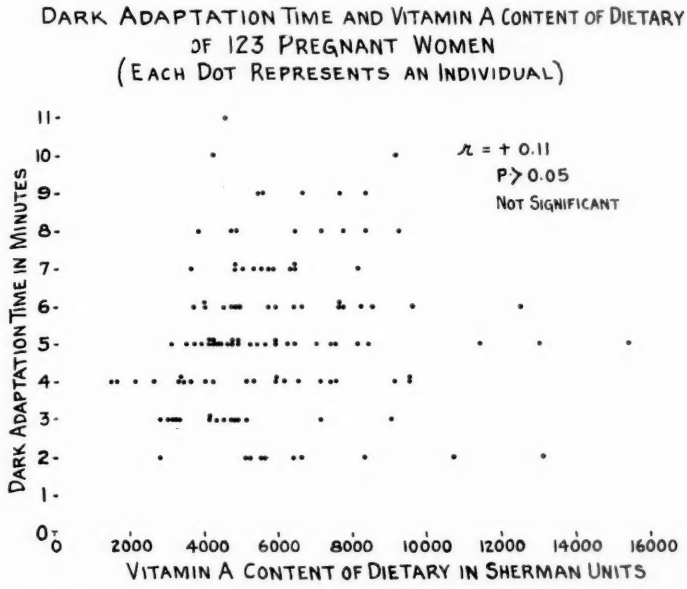

Fig. 5.—Scatter diagram showing correlation between dark adaptation time and vitamin A content of dietary of 123 pregnant women. (Each dot represents an individual.)

cernible for a higher vitamin A content of the dietary to be associated with a shorter dark adaptation time. In fact there is a slight positive correlation ($r = +0.11$) in the opposite direction, a higher vitamin A

content of the dietary tending to be associated with long dark adaptation times. However, the correlation coefficient is not statistically significant.

This type of correlation may be due to several factors. The vitamin A value of the diet may express a large proportion of carotene which may not be transformed. Other faults or variations in the physiology, of which we were ignorant, might have been present, and the human element in some instances, may have contributed to an unreliable record.

Thomson, Griffith, and others[22] state the problem succinctly when they say, "The estimation of the amount of vitamin A or its precursors in food-stuffs has not yet reached a high degree of precision; published results for any one foodstuff show a wide range of variation, and it is not possible to be certain that published results are valid for the particular foods in any one diet. In experimental studies in which large doses of concentrates are given, this is not of importance, but it is of importance when attempts are made to correlate the vitamin A or carotene content of natural foodstuffs with dark adaptation."

Since sufficient amount of fat in the diet is considered essential for the proper transference and utilization of vitamin A, we have checked the fat content of the diet against the dark adaptation time in the series. The dietary fat value requirement was 91 Gm., as it was the average value. A fat value of such requirements, or above, and a normal, or shorter, dark adaptation time were present together in 40 per cent. A deficient dietary fat value and a delayed adaptation time were present together in 10 per cent. A deficient fat value and a normal, or more rapid, time were present in 23 per cent, and the remaining group with normal fat value and delayed time present, comprised 27 per cent. Here again the relationship is not sufficiently positive to be significant.

We have endeavored to determine the effect of supplemental administration of vitamin A upon the dark adaptation time. Oleum percomorphum,* was given to a group of women who had a dark adaptation time delayed beyond the generally accepted normal of five minutes. Twenty-eight women co-operated to an extent sufficient that the results may be reported.

The vitamin A was taken in a dose of 20,820 international units per day for seven days preceding the appointment for the second reading. At this time 21 showed reductions in the dark adaptation time ranging from one to six minutes. Of the remaining 7 women, 3 showed no reduction; and in the other 4 an increase of one minute was noted in 3, and an increase of three minutes in one. A third estimation was made seven to fourteen days after the second in these seven women and an improvement not noted at the second test was present in four. The assumption is that in these cases either the absorption or utilization was slower than usual due to some unknown delay in the mechanism concerned.

Of the 10 women in the seven-minute group, 9 showed reductions and one an increase. The findings in the group showing seven-minute readings have been expressed graphically in Fig. 6.

We regret that lack of time did not permit a control series without administration of vitamin A, and the same factor prevented a study of

*Furnished through the courtesy of Dr. Warren M. Cox, Jr., and the Mead Johnson Company.

the effect of the administration on a group of women whose adaptation time was better than normal.

That vitamin A may build up resistance to infection is an allowable claim. In this respect we have noted the febrile morbidities of the puerperium in 108 delivered women of the series with the vitamin A value of the diet.

There were 13 cases in which the temperature reached 100.4° F. (38° C.), twice in any two of the first ten days post partum. Eight of these had mild pelvic infections, five following forceps, premature delivery, toxemia, and packing for postpartum hemorrhage, and three following normal spontaneous delivery. In 7 cases the vitamin A value of the diet was low, in one it was above normal. In 3 cases of pyelitis the vitamin A value was low in only one. It was low in a case of mastitis, and in one anesthetic pulmonary complication after a cesarean section. However, many women with lower values did not develop any febrile morbidity.

There were two premature deliveries, one unexplained stillbirth, and one monster. In these four instances the vitamin A value was much below normal. The diets in this group were regarded as altogether markedly inadequate.

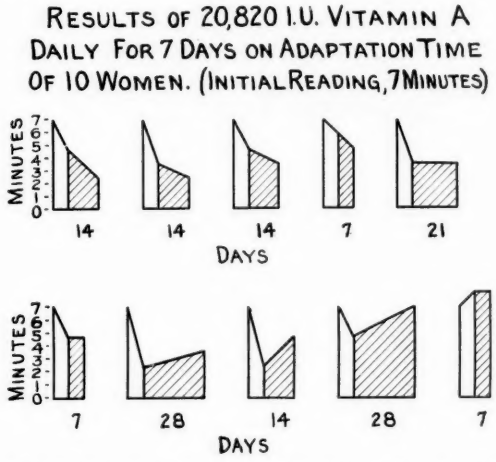

Fig. 6.—Results of administration of over 20,000 international units vitamin A daily for seven days on adaptation time of 10 women. (Initial reading, seven minutes.)

The relation of the weight of the baby to the vitamin A value of the diet permits no definite conclusions, as the series is relatively small.

In the 15 mothers of babies which weighed eight pounds or above at birth, 10 had values above 6,000 Sherman units and 15 below this figure. Of the 6 mothers whose babies weighed less than 6 pounds, only one had a dietary vitamin A value above 6,000 units.

Of the 104 babies, excluding a monster, a stillborn, and two prematures which died, 32 were on formula feeding when they were discharged from the hospital. Of the 32 mothers so represented the dietary vitamin A values were evenly divided above and below the requirement level of 6,000 Sherman units.

SUMMARY

In an analysis of the diets of 123 pregnant women, 62 per cent showed vitamin A below the requirement for pregnancy stated as 6,000-10,000 Sherman units.

The same women, together with 11 others for whom we had no food records, were tested for their dark adaptation time. Thirty-seven and one-half per cent gave readings delayed beyond the accepted normal of five minutes.

The correlation coefficient between the two types of analysis was not statistically significant.

A similar insignificant relationship was seen between fat intake and dark adaptation time.

The administration of vitamin A in concentrated form in 28 cases was followed by an improvement in the dark adaptation time in 75 per cent of the cases.

Ten of 13 delivered patients, with febrile morbidity in the puerperium, showed subnormal vitamin A intake. Many other women, however, with intakes below the requirement did not show febrile morbidity.

The series is considered too small to draw conclusions with reference to the birth weight of the baby and the mother's vitamin A consumption; nor was there any significant relationship between efficient lactation and vitamin A intake.

CONCLUSION

It appears from the above summary that while there is a marked deficiency of vitamin A content in the diet (62 per cent of 123 pregnant women), and a considerable deficiency in dark adaptation time (37.5 per cent), yet there is no close relationship between dark adaptation, the process of regaining clear vision in darkness, and the intake of vitamin A in the diet; nor between vitamin A intake and certain obstetric factors in a short series of cases.

We are grateful to Mrs. Anna DePlanter Bowes, Miss Elizabeth Pitney, and Dr. Olive Hoffman, for their valued technical assistance, and to the social service and dietary staffs of the two hospitals where the study was conducted, for their cooperation.

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VITAMIN A IN PREGNANCY

I. Average Capacity According to the Feldman Adaptometer

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THE identity, chemistry, physiology, and pathology of vitamin A have been well studied and numerous reports are found in the literature, but only in recent years (1934) have blood assay and photometric methods of determining vitamin A capacity been generally available. Since that time, the vitamin A levels of numerous groups of patients have been studied, although mostly under variable methods and conditions, not including pregnancy.

It has been our purpose in this study to attempt to establish via photometric tests the average vitamin A capacity through pregnancy, and the frequency, degree and significance of deviations from this "normal."

PRINCIPLES

The fat soluble vitamin A is a derivative of the carotinoid group of pigments from plants from which the animal body is able to metabolize vitamin A. This vitamin is stored in the body principally in the liver, so that abnormalities of digestion, anemia,[1] and liver disease[2] may interfere with absorption and storage of the vitamin. Thus actual vitamin A deficiency may arise in association with vomiting, chronic diarrhea, biliary duct obstruction, pancreatic dysfunction, celiac disease, etc.

The process of achieving more or less vision in the dark, called "dark adaptation," is dependent upon supply or level of vitamin A, and it is established that one of the earliest functional changes due to vitamin A deficiency is decreased ability for dark adaptation resulting in night blindness,[3] commonly experienced as unusual difficulty in locating seats in motion picture theaters, and in dangerous temporary loss of vision while driving an auto against another's headlights.

Persons showing latent or actual night blindness are also apparently predisposed to urinary infection and calculus,[1] respiratory infection, certain skin affections[4] and possibly to puerperal infection.[5]

Light enters the eye and falls upon the retina where it is absorbed by the photosensitive visual purple of the rods which are concerned with vision under dim illumination. The visual purple photosensitive pigment is a protein combination with vitamin A, and with absorption of light is broken down, initiating the nerve impulse of sight in darkness. However, normally, this visual purple is rapidly resynthesized from reserve of vitamin A, the rapidity being dependent upon the amount of vitamin A available. Ample vitamin A therefore means rapid dark adaptation as well as good night vision, but deficiency of vitamin A results in delayed adaptation or night blindness.

If the visual purple is bleached or decomposed by a definite and constant quality and intensity of light for a standard period of time in a dark room, then the rapidity of the eyes to recover ability to see a definite intensity of dim light becomes a measure of the person's dark adaptation, and consequently his vitamin A level of the body, the recovery period being designated as the dark adaptation time. Various apparatuses have been devised to establish adaptation time, including the questionable biophotometer,[6] which has proved variable by reason possibly of insufficient light to completely bleach the visual purple; rheostat light control which

changes color of the light (as well as intensity); difficulty in observing patient; and interference of macular vision.

METHOD

The patient is placed in a totally darkened room and the eyes exposed to the adaptometer's bright standard intensity of light for exactly three minutes. This light is then turned off, and in its place a constant dim linear light of definite intensity appears 20 degrees off the macula where the rods predominate. A stop watch is started and the patient told to tell the examiner as soon as the dim linear light becomes visible, the time interval being recorded. As a check upon the patient, the angle of the dim light is changed from horizontal to vertical or vice versa and the patient asked to indicate in which direction it is pointing. This prevents false readings in that it proves to the examiner that the patient has actually seen the light. The adaptation time is then read in minutes and seconds.

With this instrument it has been determined that a light threshold adaptation time of five minutes or over is pathologic and indicative of vitamin A deficiency, whereas an adaptation time below five minutes is evidence of normal vitamin A level. We have found the Feldman adaptometer particularly satisfactory for prenatal observation because of the ease of operation, comparative rapidity of the test, and fairly uniform results according to frequently repeated tests on our normal pregnancies.

MATERIAL

The Preston Retreat is an endowed institution for the confinement of "indigent married women of good character" who are residents of Philadelphia and Delaware Counties. Capacity is limited, and because there are always more applicants than can be accepted, a certain degree of selection is possible. There are no colored patients and the majority are of so-called American stock, factors which result in a rather high type of clinic patient. This we feel is important, representing the largest proportion of women in the country, namely, the lower middle class.

Medically, the patients are carefully and adequately followed throughout their pregnancy and confinement, and social service cooperation is exceptionally good, including home visits to every patient.

This study was begun in March, 1939, upon a group of 200 uncomplicated patients, one-third nulliparas and two-thirds multiparas, all of whom have been delivered. Adaptation times were taken by the same technician between 9:30 and 11:30 A.M., daily, at various intervals throughout pregnancy and upon many at the six weeks' post-partum visit, and some much later. All patients who showed an abnormal adaptation time, i.e., five minutes or over, were examined by an ophthalmologist to determine whether the high reading might be due to ocular pathology. It may be stated here that none was found.

RESULTS

Fig. 1 shows the average prenatal and postnatal adaptation times of 200 registered clinic patients as derived from 880 tests. The highest and lowest readings were, respectively, 480 and 15 seconds, but the greatest divergence in any one case was 345 seconds (from 6 minutes—45 seconds to 1 minute). There were only 18 (9 per cent) readings of five minutes or over and 4 (2 per cent) of these were accounted for by women with high primary single, presumably false, estimates, probably due to the subjective nature of the procedure since subsequent tests were all low. On the other hand, 3 patients (1½ per cent) gave original low readings followed by increases approaching or over five minutes on only one occasion, possibly indicating a pregnancy trend toward avitaminosis A, but more likely subjective temporary fatigue or emotion. The general downward or improvement trend may be attributed to improved prenatal condition, or less likely to the influence of the summer season during which the latter half of the tests were performed.

Fig. 2 shows the distribution of reading by weeks, not including 14 observations as late as eight to thirty-eight weeks post partum. The open circles repre-

sent adaptation times of the first 100 cases, and the solid circles indicate readings from the second 100 patients, showing a tendency to lower results, i.e., higher vitamin A as pregnancy advances.

Forty-four per cent of the "normal" patients gave repeated adaptation times not varying more than sixty seconds, excepting the first reading, among which 4 per cent were almost constant. The remaining 56 per cent varied more than sixty seconds, but not nearly to the degree of the pathologic and borderline groups described later.

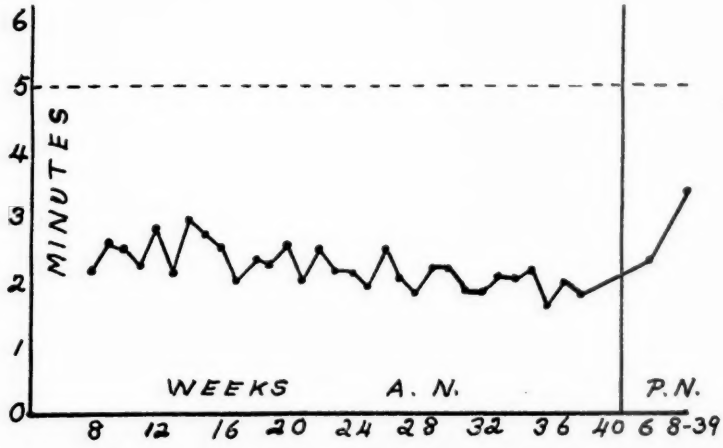

Fig. 1.—Mean dark adaptation of 200 average pregnancies, showing increasing vitamin A capacity.

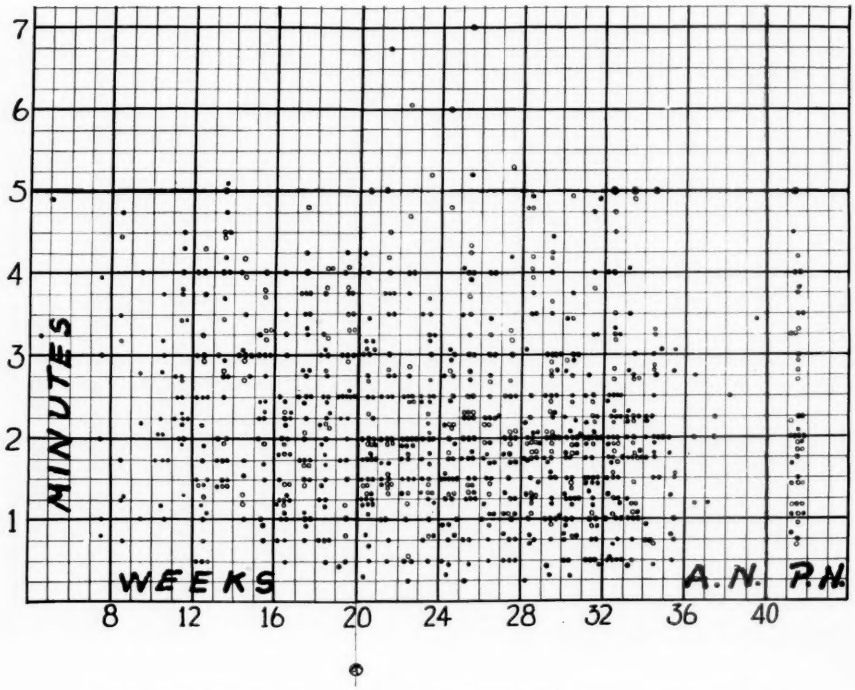

Fig. 2.—Distribution by gestational weeks of 880 adaptometer readings.

Fig. 3 includes the entire curves of 6 cases (3 per cent) considered pathologic, based on 2 or more readings of five minutes or over, apparently not entirely due to pregnancy, and none of serious degree or constantly above the abnormal limit.

Fig. 4 shows 8 cases (4 per cent) of temporary borderline abnormal type, each characterized as those of the preceding group by rather wide excursions, difficult to explain.

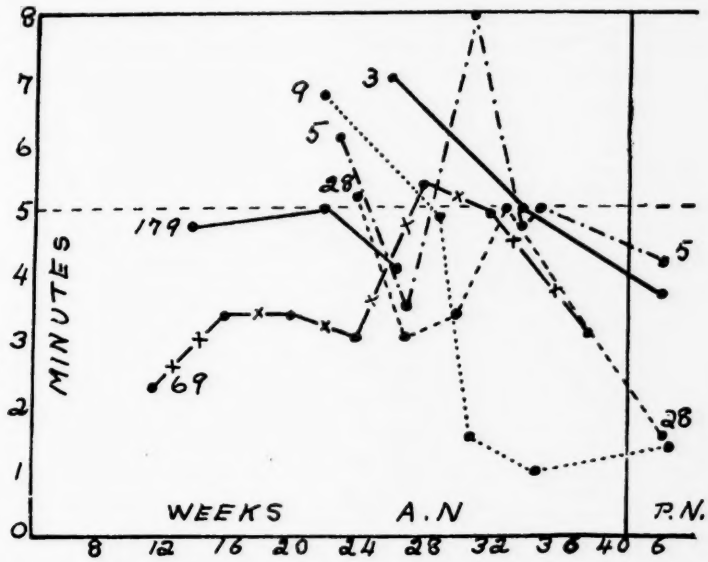

Fig. 3.—Curves of 6 (3 per cent) pregnancies with delayed adaptation times of five minutes or over, 2 or more times.

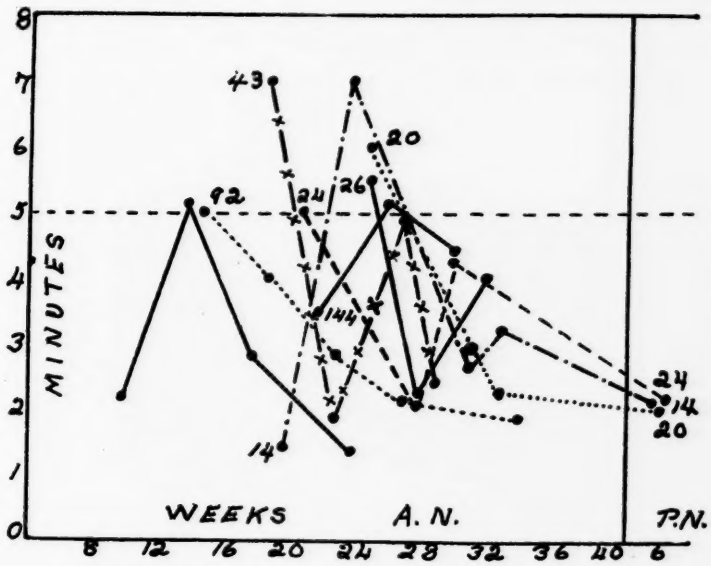

Fig. 4.—Curves of 8 (4 per cent) "borderline" pregnancies with at least one delayed adaptation time about five minutes, excluding 4 cases of single primary high (false) readings.

In our series, there was no apparent relation between vitamin A deficiency and complications of pregnancy, labor and the puerperium, particularly with regard to respiratory, urinary, and puerperal infection.

It is clear that single test estimations of vitamin A level in patients are acceptable only if pathologic adaptation times are rechecked and verified several times within a short period. This should apply particularly where therapy is contemplated and again in any attempt to establish deficiency percentage by running single tests on large numbers of patients. It may also be added that for obvious reasons, the intelligence of the patient is a big factor, tending in single tests to produce a high amount of apparent but unreal vitamin A pathology.

SUMMARY AND CONCLUSIONS

1. Two hundred registered pregnant women in the clinic under good prenatal control were repeatedly tested for vitamin A capacity by the Feldman adaptometer.

2. Nine per cent showed at least one reading above five minutes, but only 3 per cent showed repeated abnormal readings and were judged deficient in vitamin A, and 4 per cent were "borderline."

3. Vitamin A deficiencies occurring in average pregnancy tend to be mild, and not entirely related to pregnancy.

4. There is a general tendency to improvement in normal vitamin A status during pregnancy, as well as less frequent deficiency, due either to the summer season, or most likely to good prenatal care.

5. There were no significant medical and/or obstetric complications among the small number of deficient women.

6. Many more pregnancies must be studied before absolute reliance may be placed upon a subjective test for vitamin A.

In our series we made use of the adaptometer designed by J. B. Feldman,[7] M.D., and provided by Wm. J. Ezickson, M.D., to whom the authors are also indebted for criticism and advice.

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Pagniez, Ph.: The Treatment of Pruritus Vulvae by the Local Injection of Histamine, Presse méd. **47:** 1359, 1939.

The writer reviews Lavandhomme's experience with the use of local injection of histamine for pruritus vulvae. In 5 of 6 cases persisting from several months to several years, the injection of histamine produced rapid and apparently lasting relief to the patient. Lavandhomme uses 1 c.c. ampoules, containing 0.005 Gm. of histamine bichlorhydrate. At the first visit he makes 20 intradermal injections in the labia majora. During the following visits, the site of the injections is progressively extended toward the labia minora and the vaginal mucosa. He observed in 2 cases the disappearance of early atrophic or kraurotic vulvar lesions.

The author feels that this mode of treatment may well be tried in the more rebellious cases of pruritus vulvae.

Clair E. Folsome.

PREGNANCY PYELONEPHRITIS IN RELATION TO RENAL DAMAGE AND HYPERTENSION*

A Clinical Study of 45 Cases of Pyelonephritis More Than Five to Ten Years After the Infection

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(From the Urological and Toxemia Services of the Boston Lying-in Hospital)

THAT a causal relation should be recognized between pyelonephritis and renal insufficiency and hypertension is indicated by recent publications. This interrelation is further confirmed by autopsy findings, which show either healed or still active pyelonephritic lesions in a high percentage of hypertension cases. This belated recognition of what seems to be a fact is explainable chiefly on the ground of chronicity of pyelonephritic lesions, their tendency to persist or to recur, and their progressive nature, which makes an estimate of the degree of damage of the kidney by the initial injury more obvious long after injury than at the time it occurs. The picture has been further confused and recognition of injury to the renal cortex missed, particularly by urologists, because attention has been concentrated on, and a causal significance assigned to, the more obvious and easily demonstrable injuries and defects of the conduction channels of the kidney, the pelves, and ureters. Until more recent years, there has been no provision for continuity of observation of a case by the same physicians over the long course which we now recognize that pyelonephritis runs.

Both in pregnancy infections of the urinary tract and in those in the puerperium there is little evidence, in most cases, of renal insufficiency, and where such insufficiency has been demonstrated, there is prompt return of the kidneys to apparent normal function in pregnant women. These apparent facts tended to strengthen the point of view that pyelonephritis is a transitory affection. Obstetric and urologic practice have been dominated by this point of view to such an extent that preservation of the fetus, even in severe cases of pyelonephritis of pregnancy, has been made paramount unless immediate danger of disastrous results to the mother was indicated. The newer concept of the severity of remote effects of pregnancy pyelonephritis now threatens a reversal of policy. Some writers are prepared to advocate interruption of pregnancy on evidence which obstetricians consider inadequate (Peters[1]). The strongest evidence so far

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produced for making a practice of routine interruption of pregnancy for pyelonephritis is from medical data obtained from the study of terminal hypertension cases and autopsy material.

This policy, if adopted now, would be unsupported by evidence of the state of health of these women with pregnancy pyelonephritis over long intervals admittedly existing between the initial injury and the terminal medical surveys and autopsy examinations. Does pyelonephritis shorten the lives of such women or merely modify the data on the death certificate? Do they evidence ill health throughout their lives, after pregnancy infections, or are their kidneys adequate for normal living in spite of injury until terminal changes, possibly due in part to other factors, end in the development of renal insufficiency or rise in blood pressure which quickly closes the story somewhere near the average age for death for women? In what percentage of women who have had pyelonephritis in pregnancy, and in what types of the disease, does complete recovery from the injury occur? In what percentage of the cases has there been set in motion, as a result of infection, those vicious factors which accomplish their destruction in the course of a few years? Until some of these questions have been answered through clinical study of apparently healthy women who have had the disease, a radical policy of interruption of pregnancy for pyelonephritis is no more logical than a policy which preserves the pregnancy at any cost to the mother short of death.

Hage[2] furnishes striking data on pyelonephritis and contracted kidney in autopsy material. In 9,888 routine autopsies performed between 1931 and 1937, 598 patients showed pyelonephritis. Sixty-nine patients showed contracted kidneys. Pyelonephritis was about equally distributed among women and men. Contracted kidney was found more often among women than men. The commonest causal factor in men seemed to be prostatism, and pyelonephritis was found more often in later life. In women, he considered that pregnancy accounted for the occurrence of the condition in a large number of cases. There was evidence that prostatism in men and pregnancy in women were responsible for a high percentage of the pyelonephritis which he found at autopsy, and these two conditions seemed to be the main diseases through which numerical balance in frequency of occurrence of pyelonephritis between the sexes was maintained.

In view of the general considerations above, it has seemed advisable to investigate a group of apparently healthy women from our clinic, the nature of whose illness at the time of the initial pyelonephritis was known to us, since they were cared for in our hospital, to determine whether there was evidence of renal insufficiency and hypertension.

The material employed in this study consisted of 45 cases of pregnancy pyelonephritis, in which the pyelonephritis occurred from five to ten years before the investigation was undertaken. These cases represent the usual variation in incidence of the disease. Some were ante-partum cases, some were post-partum cases, and in others there were manifestations of the infection both in the ante-partum and the post-partum state. In some, there were no further pregnancies after the infected pregnancy. In others, there were from one to five subsequent pregnancies. In some of the subsequent preg-

nancies, there were manifestations of infection. In others, there were subsequent pregnancies without signs of infection.

The cases were divided into three groups, according to severity of the pyelonephritis symptoms demonstrated. Group I consisted of 14 cases in which there were pyuria, bacteriuria, and little or no febrile manifestations. If fever occurred, it was of but a few days' duration, after which the patient continued in apparent good health, but remained for the most part infected throughout the remainder of the pregnancy. Group II consisted of those cases in which there was some febrile reaction and more severe symptomatology, but the patients all were tractable to treatment and finished the pregnancy in good general condition. There were 12 cases in this group. Group III consisted of 19 cases. These were all severe febrile reactions to the infection and most of them required cystoscopic treatment and even induced labor before the subsidence of the acute symptoms was obtained. Unilateral infections were present in all the groups. One case was included in which a post-partum infection proved to be only cystitis, resulting from catheter management of bladder difficulties which followed delivery. In this case, it is of interest to note the normal response to all tests, in contrast to a tendency for some unilateral mild cases to show evidence of subnormal response to some or all tests employed. There were no cases in which there was evidence from pyelographic study of the condition of the kidneys previous to the childbearing period. No cases were included in which it was probable that pre-existing renal pathology was present previous to pregnancy, as judged from the appearance of the pyelography at the time of this survey. Three cases were in the early months of a subsequent pregnancy when re-examined. In three cases, definite toxemic symptoms occurred in the course of the pregnancy, in addition to pyelonephritis. One of these cases was seen less than five years after infection, but was included because of a desire to contrast the present condition of the patient with the pyelonephritis group as a whole. The other two toxemic patients had already died.

Method of Study Employed

As far as it was possible to enlist the cooperation of the patient, all patients were tested by seven measures. These were: (1) Sufficient number of blood pressure readings to determine hypertension; (2) albumin determination on catheter urine; a wet sediment was also examined for pus, erythrocytes, and bacteria; (3) stained catheter urine sediment to determine bacterial content; (4) culture from catheter urine; (5) intravenous phenolsulfonephthalein excretion in four fifteen-minute periods for a total excretion period of one hour; (6) intravenous diodrast with special attention to the time at which the best plate appeared in the course of the pyelography; (7) nonprotein nitrogen (whole blood) determination. In three instances, cystoscopic study and separate determination of function of the kidneys was done. Sulfanilamide therapy was employed in an attempt to clear the infection, so that a redetermination of the renal adequacy might be made after the infection had been cleared. In one of these cases, a rise in nonprotein nitrogen accompanied the administration of sulfanilamide and caused discontinuance of the treatment before the infection had been cleared. Similar behavior was noted in another case of renal deficiency, not in this series, when sulfanilamide was administered.

GROUP I. FOURTEEN CASES STUDIED

Grouped according to time of infection in pregnancy:

Ante-partum infections	4
Post-partum infections	7
Ante-partum and post-partum infections	3

2 patients showed pre-eclamptic symptoms in addition to pyelonephritis.

Grouped according to parity:

First pregnancy	5
Second pregnancy	2
Third pregnancy	1
Fourth pregnancy	2
Fifth pregnancy	2
Sixth pregnancy	1
Not recorded	1

Grouped according to side involved: 6 cases cystoscoped.

2 ante-partum unilateral; 1 right, 1 left sided.
2 post-partum bilateral
2 both ante-partum and post-partum bilateral (1 cystitis only)

Grouped according to subsequent pregnancies:

Sterilized for apparent renal deficiency soon after delivery	1
1 subsequent pregnancy (One had infection but mild symptoms)	2
2 subsequent pregnancies	3
3 subsequent pregnancies (without infection)	1

The remaining women had no subsequent pregnancies.

Cystocele was present in 2 who were wearing pessaries. A third patient had been operated upon for cystocele. This percentage of cystocele is noteworthy, because for many years we have been checking residual urine to determine bladder condition, and it is rare that cystocele is noted near to delivery. The finding is in accord with the point of view expressed by gynecologists that cystocele develops late, although due to birth canal injury.

Blood Pressure Findings.—Only 3 patients, and these not the pre-eclamptics, had blood pressures above 150/90. One with a reading of 160/92 had had ante-partum infection with a single pregnancy, her fifth. She had a normal phthalein excretion, concentrated to 1.018, and there was no evidence of infection at time of the examination. She had had two pregnancies without recurrence of the infection. The original infection was bilateral. Later the patient was operated upon for renal calculus elsewhere, and finally had a thyroidectomy. A second patient had an infection with the fifth pregnancy, but the infection did not occur with subsequent pregnancies. The blood pressure was 190/130. There was a deficiency in the phthalein output. The urine was concentrated to 1.024. She was still infected, and there was unsatisfactory filling of the kidneys and ureters on intravenous pyelography, but no symptoms of any kind. The third patient was infected in her second pregnancy. She had had no subsequent pregnancies but was considered infected, with much pus and mixed infection. The urine was concentrated to 1.022. Later she was found (elsewhere) to have stones and hydronephrosis of the left kidney. The right kidney was uninfected at the time of study previous to lithotomy for the stone.

Concentration of Urine Test.—Three patients concentrated their urines to 1.025 or above. Eleven patients did not concentrate to 1.025.

Nonprotein Nitrogen.—In none of the cases was nitrogen retained. The highest figure obtained was 36 mg. per 100 c.c. of blood (whole blood method).

Intravenous Pyelography.—Eight patients had intravenous pyelography. In one, the cystitis case, the best plate was obtained at five minutes after injection of the

dye. In 6, the best plate was seen at fifteen minutes, and at thirty minutes in the other. A definite reluctance to fill on the side with the most severe infection was noted in all of these cases, if there was any difference at all between the kidneys.

Intravenous Phthalein Test.—In 8 of the 14 cases, there was evidence of delay in output of the dye, so that the first fifteen-minute output was below 25 per cent and was usually below that of the second, and sometimes of the third, interval of excretion. The excretion curve for the whole group is indicative of this relation (Fig. 1).

Albumin.—Albumin was not present in the catheterized urines of any of this group.

Wet Unstained Sediment Examination.—Only one of the 14 patients showed frank pus in the urine. Red blood cells were not noted. Five patients showed bacteria in sufficient numbers in the unstained smear to be considered to represent infection. Cocci are less readily recognized by this method than bacilli.

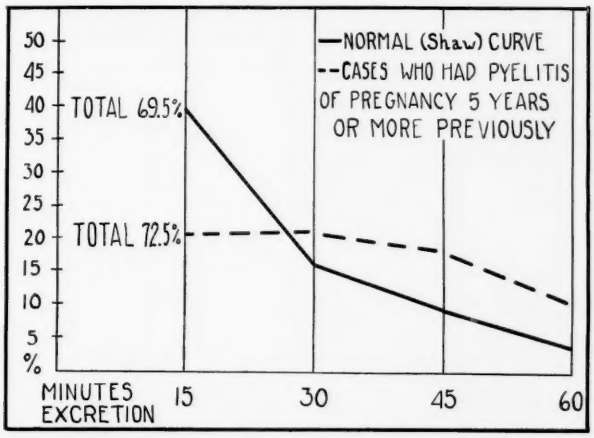

Fig. 1.—A composite chart of phenolsulfonephthalein excretions for the cases in this series. It is to be noted that the total secretion is not diminished for the group as a whole. There is, however, flattening of the curve by delay of the major portion of the output beyond the first fifteen minutes.

Stained Preparation From the Sediment and Culture.—Stained sediment and culture agreed in establishing the diagnosis in 5 patients as being infected and 2 as uninfected. Three cases yielded bacilli, culturing *B. coli;* 1 a mixed infection of *B. coli* and staphylococcus; and 1 staphylococcus only. Cultures showed 7 other cases to contain bacteria. In stained smears, rare bacteria were sometimes found. These cases showed the following findings:

Micrococcus catarrhalis	2
Rare colonies of *Streptococcus fecalis*	2
Staphylococcus albus and Döderlein's bacillus	1
Gram-positive and gram-negative unidentified bacilli	1

These six cases were considered as probable contaminations and not infections.

Gross evidence of abnormality, as shown by x-ray and intravenous pyelography.

Calculus	3
Pelves large and ureters tortuous	2
Either small renal shadows or caliceal evidence of contracted kidneys on one or both sides	4
Very poor filling of both pelves and ureters	2
Ureters filled so far down toward bladder as to suggest obstruction	2
Aberrant vessel small hydronephrosis	1

In recording these results of x-ray, the numerous lesions noted occurred in 4 of the 8 cases in which pyelography was done.

In 3 outpatient cases and one house case, the infection was cleared without difficulty by administration of sulfanilamide. One patient in this group, in whom a questionable diagnosis of pre-eclampsia, in addition to pyelonephritis, had been made during pregnancy, and who later had moderate renal deficiency to phthalein excretion, showed a rise of nonprotein nitrogen from 35 mg. per 100 c.c. of blood to 58 mg. on the third hospital day of administration of 40 gr. daily of sulfanilamide without concentration of urine. The nonprotein nitrogen began to decrease on discontinuing the drug and returned to normal within the next few days.

GROUP II. MODERATELY SEVERE INFECTIONS (12 CASES)

Grouped according to time of infection in pregnancy:	
Ante-partum infections	6
Ante-partum and post-partum infections	6
None were toxemic	
Grouped according to parity:	
First pregnancy	4
Second pregnancy	3
Third pregnancy	2
Fourth pregnancy	2
Eighth pregnancy	1
Ninth pregnancy	1
Tenth pregnancy	1
Eleventh pregnancy	1
Twelfth pregnancy	1
Grouped according to side involved:	
Bilateral	5
Unilateral	5
Not recorded	2
Grouped according to subsequent pregnancies:	
Without recurrent pyelonephritis	1
Died of cancer of lung soon after infected pregnancy. It was noted that the kidneys appeared to be normal.	1
Record of 5 infected pregnancies, subsequent pregnancy with pyelonephritis cared for elsewhere, 3 other pregnancies were unknown	1
3 subsequent pregnancies, 2 with elevated blood pressure	1
No further pregnancies	6

Blood Pressure Findings.—Four of the 12 patients had blood pressure readings above 150/90 at the time of examination. The first had a pressure of 150/100. She was primiparous at the time of pyelonephritis, with no subsequent pregnancies (1930), and showed delayed output of phthalein, concentrated to 1.022. There were albumin, pus, and a definite infection with *B. coli.* X-ray films made elsewhere reported her as showing chronic pyelonephritic changes. The second case, 160/100, showed normal phthalein excretion, concentrated to 1.027, was uninfected, was a bilateral pyelonephritis in 1931 in her third pregnancy. She had three subsequent pregnancies, one of which was reported from another hospital to have been accompanied by a rise in blood pressure. In the following pregnancy she also had high blood pressure. The third patient, 156/94, had normal phthalein output; concentrated to 1.026, was uninfected, and had a single infected pregnancy, with both sides involved, in 1930. There were no subsequent pregnancies. The fourth patient, 160/100, refused intravenous phthalein test; concentrated to 1.026, was infected in the fourth pregnancy, 1929, and had no subsequent pregnancies. She now has a stone.

Concentration Test.—Three of 8 patients tested did not concentrate to 1.025. All eight concentrated to 1.020.

Nonprotein Nitrogen Test.—Six patients tested. All were normal.

Albumin.—Albumin was present in but 1 patient of the 12. This patient is the first one in the preceding paragraph on blood pressure findings.

Wet Unstained Sediment Examination.—Two of 9 patients examined showed pus, and 1 other showed bacteria. No red cells were reported.

Stained Smear Preparations and Cultures.—Three of 9 patients showed bacteria and 6 were negative. Of the 3 with bacteria, 2 were bacilli and 1 coccus. Of the 10 patients in whom there were cultures, 2 showed *B. coli* and 1 *Staphylococcus aureus.* These were the same patients who were reported positive in stained smears. Seven were negative to culture. Of the 4 hypertension cases, 3 were uninfected. There were no doubtful infections or questions of contamination in these patients.

Intravenous Phenolsulfonephthalein Excretion.—Excretion of phenolsulfonephthalein was tested in 6 of the 12 patients. It was normal in 4 instances and abnormal in 2. The readings in the first of the patients considered abnormal were 10 per cent, 15 per cent, 35 per cent, and 10 per cent for a total of 70 per cent in one hour after intravenous injection of the dye. In the other patient, the excretion was 20 per cent, 30 per cent, 25 per cent, and 10 per cent for a total of 83 per cent. These patients show delay and not a deficiency of excretory ability.

Intravenous pyelography was done in but 5 cases. In 2, the pyelography was done elsewhere and was reported negative. In the 3 patients in whom we did pyelography, there were stone and kink in one, stone in another, and in the third patient there was poor filling of the kidney which had been the site of a unilateral infection.

GROUP III. SEVERE INFECTIONS, 19 CASES

Grouped according to time of infection in pregnancy:	
Ante-partum infections	9
Post-partum infections	2
Ante-partum and post-partum infections	7
Not stated	1
Grouped according to parity:	
First pregnancy	11
Second pregnancy	1
Third pregnancy	3
Fifth pregnancy	1
Ninth pregnancy	1
Twelfth pregnancy	1
Unknown	1
Grouped according to initial lesion (cystoscopically controlled):	
Bilateral lesions	8
Unilateral lesions	7

There was stone also in 1 of the patients at the time of initial examination, congenital absence of 1 kidney in another, and in 1 unilateral case infection was confined to the left side.

Grouped according to subsequent pregnancies:	
1 normal pregnancy	9
Now pregnant (one at 3 and other at 4 months, without trouble)	2
2 pregnancies (one abortion from pyelonephritis, the other uninfected)	1

Three of these patients had pregnancy toxemia in addition. One patient with toxemia and bilateral pyelonephritis, both ante partum and post partum in the first pregnancy, 1930, died of hypertension, "chronic nephritis" and renal failure in 1936. A second patient had ante-partum pyelonephritis and toxemia in the first pregnancy, 1931, had a second pregnancy which was said to be free of complications, and died of acute cardiac failure. She collapsed and died suddenly at a relief station in 1937. The third patient, who has not rightly been included in this group, since but three years have elapsed since her infection, was included that we

might have the data on a case si[illegible]o the two who died, but at a time antedating death. She was primiparous, wi[illegible]eral infection, in 1936. There have been no subsequent pregnancies. Blood pre[illegible]ure, 165/106. Phthalein output 10 per cent, 13 per cent, 9 per cent, and 7 per cent for a total of 39 per cent in one hour after intravenous injection of dye. Nonprotein nitrogen was 40 mg. per 100 c.c. of blood, by whole blood method; concentrated her urine to 1.016. She is still infected with hemolytic *Staphylococcus aureus* and showed three-plus albumin and hyaline casts. There was no retention of the intravenous media in the kidneys sufficient to cast a shadow at all, with only a trace of dye appearing at thirty minutes, but insufficient to outline any part of the kidney pelves accurately. This patient was studied intensively at the Beth Israel Hospital.

The findings were as follows: She was 28 years old; hypertension and swelling of the legs were apparent three months following delivery. On rest in bed, the blood pressure readings ranged near normal; the highest reading was 135/70. The edema and discoloration of the legs persisted even though she remained in bed.

Laboratory Data.—During the hospital stay, on catheter specimens, patient showed very slight trace to trace of albumin with 3 to 5 white blood count and a rare red blood count. Blood was normal in all respects; red blood count 4.18, hemoglobin 77 per cent, white blood count 8,700, 66 per cent polymorphonuclears, 27 per cent leucocytes, 3 per cent large mononuclears, 3 per cent eosinophiles. On admission, nonprotein nitrogen was 35 mg. per cent; following sulfanilamide therapy it rose in three days to 58 mg. per cent; after sulfanilamide was discontinued, nonprotein nitrogen slowly fell and on discharge was 43 mg. per cent. Hinton and Kahn negative. Blood sulfanilamide level was 3.4. Sterile catheter specimens showed 0-4 gram-negative bacilli per field. Cultures were negative. Concentration dilution test: Patient concentrated between 1.004 and 1.010, diluted between 1.002 and 1.008. Urea clearance test: Clearance 45.2 per cent in the first specimen and 29.7 per cent in the second specimen. Phenolsulfonephthalein, at cystoscopy, in the right ureter there were 10 c.c. with less than 2.5 per cent phenolsulfonephthalein; left, 5 c.c., with less than 2.5 per cent phenolsulfonephthalein. Intravenous phenolsulfonephthalein, first specimen, 100 c.c., off color; second specimen, 90 c.c., 6 per cent; third specimen, 30 c.c., 1 per cent; fourth specimen, 95 c.c., 3.5 per cent. On cystoscopy, the bladder urine showed a slight trace of albumin, was alkaline, and showed 2 to 4 red blood cells per field. Right ureter showed albumin, 5 to 7 red blood cells per field in the sediment. Gram stain of urine from bladder, right and left ureters showed no bacteria.

X-rays.—Kidney, ureter, and bladder essentially negative. Retrograde bilateral pyelography showed no demonstrable abnormalities in the calices, pelves, or ureters.

Clinical Course.—Concentration and dilution tests, urea clearance, and intravenous phenolsulfonephthalein were done. Following these the patient had a menstrual period. A later cystoscopy and pyelography were done. Bladder mucosa was dull. Extensive cystitis cystica over the trigone. Fourth phenolsulfonephthalein showed appearance time three and one-half minutes, both ureters. There was no residual. Following these studies, the patient was given 40 gr. of sulfanilamide, daily. On the third hospital day, the nonprotein nitrogen rose to 58 and sulfanilamide was discontinued and the nonprotein nitrogen began to decrease. Catheter specimen showed no bacteria. Culture was negative. Patient was discharged on the sixteenth hospital day, to be followed at the Boston Lying-in Hospital.

Grouped According to Blood Pressure Readings.—The blood pressure readings for this group are interesting. There were but 3 cases in which the blood pressure reached above 150/90 and those were the 3 patients who had a combination of

pyelonephritis and toxemia. Twelve patients showed blood pressure 120/or under. Three showed blood pressures below 100/000. These findings are particularly interesting, since these cases represent the most severe forms of pyelonephritis of the group studied. The low blood pressures were obtained in women who were ambulatory and living apparently normal lives.

Concentration Tests.—All of 17 patients (excluding the two patients who had died) concentrated their urines below 1.025, except 1 patient. That patient was a post-partum bilateral pyelonephritis case which still shows infection with *B. coli.* She was infected after her third and last pregnancy. Her intravenous phthalein test showed 0 per cent, 14 per cent, 28 per cent, and 22 per cent, for a total of 64 per cent in one hour after intravenous injection. She could hardly be considered to have normal kidneys.

Nonprotein Nitrogen Test.—All of 14 patients tested, except the living patient with toxemia were within the normal limits for nonprotein nitrogen readings. This patient with a reading of 40 mg. per 100 c.c. of whole blood could not be considered other than at the upper limit of normal.

Albumin.—Albumin was present, one-plus in 5 of 15 patients tested and three-plus in the eclamptic patient.

Wet-Stained Sediment Examination.—Pus was reported in 4 of 16 patients examined. Bacteria were noted in 5 patients as bacilli and in 1 as cocci. There was 1 patient in whom red blood cells were reported.

Stained Smear Preparations and Cultures.—Stained preparations in 16 patients showed 7 to be positive and all these were bacilli. Cultures were reported in 12 patients. Six patients were reported negative and 6 gave positive growths. Of the 6 positive growths, 5 were bacilli and 1 staphylococcus. There were 2 patients in whom small growths were thought to be contaminations and not to represent infection. Two patients showed different organisms in culture and stained smear preparations. Short bacilli grew out as cocci.

INTRAVENOUS PYELOGRAPHY, 10 CASES

Very poor, indistinct, inadequate filling	5
Normal pyelography, except for delayed filling	2
Poor outline of one kidney, that infected in pregnancy	1
Contracted kidney, that infected in pregnancy	1
Hydronephrosis, that infected in pregnancy	1

The best plate appeared about fifteen minutes after injection of the skiodan in 7 patients, at thirty minutes in 1, and the concentration of the dye was too weak to show outlines of pelves and calices in 2.

Intravenous Phenolsulfonephthalein Output.—In the 16 cases studied, the normal ratio of excretion of the dye, in which the initial fifteen-minute output reached at least 25 per cent, was present in but 3 of the 16 cases studied. All the remainder were below normal, or showed abnormal distribution of the dye among the four fifteen-minute periods, with a low initial output followed by increasing amounts of output in subsequent quarter-hour periods. This is indicative of delay in excretion. Three of the cases totaled less than 50 per cent for the hour of excretion. On the whole, the total excretion was not subnormal, but the chief abnormality was delay in output.

DISCUSSION

A summation of the data which have been presented indicates that particular attention should be paid both to parity and to whether the infection was ante partum or post partum, in estimating the probable severity of the patient's reaction to infection. As appears in the data here presented a definite relationship of these two factors to the degree of late damage which the patient will show after the lapse of years arous patients. In *Group I,* those which are characterized as mild can be established. Twenty of the 45 cases reported here are primip-

infections, but 5 of the 14 patients are primiparous. In the severe cases, 11 of the 19 cases occurred in primiparas. It has been stated (Crabtree, Prather and Prein[3]) that in multiple infected pregnancies the pyelonephritis which occurs in gestations subsequent to the initial infection is likely to be less severe, if febrile at all, than the initial infection.

It has been noted by many writers that the post-partum infections are less severe than ante-partum infections. In this series, 7, or 50 per cent, of the mild cases were post-partum infections, 3 were combined ante-partum and post-partum infections, and 4 ante partum. In the moderately severe cases, there were 6 ante-partum infections and an equal number of combined ante-partum and post-partum infections. In the severe cases, 9 cases were ante-partum, 7 were combined ante-partum and post-partum infections, making a total of more than 80 per cent of the group in which pyelonephritis during pregnancy was present and 2 patients showing only post-partum infection. If these figures are combined with the figures on parity, the conclusion is forced upon us that the most severe infections in association with pregnancy are in primiparas and in the ante-partum pyelonephritis.

No clean-cut evidence is produced here to indicate to what degree subsequent pregnancies increase the possibility of further damage to the kidneys of pregnant women. There seems to be evidence of voluntary limitation of further pregnancies among these women. Women who have suffered this disease cannot be blamed for reluctance to tempt fate a second time. Of the mild infections, 7, or 50 per cent, had no further pregnancies. Six of the 12 with moderately severe infections, also 50 per cent of the patients, had no further pregnancies, and 12 of 19 with severe infections had no subsequent pregnancies. Total figures indicate that 23 of the 45 patients with pyelonephritis had no further pregnancies. One patient had been sterilized, another died too soon for pregnancy to have taken place, leaving approximately one-half of the patients as a group in which pregnancy did not occur after the infected gestation.

Where pregnancy did take place subsequent to pyelonephritis, there is doubtful evidence of the significance of the following pregnancies in producing serious results, as noted in the body of the evidence from this series of patients. In 9 of the patients, there was 1 pregnancy which was apparently normal. Out of a total of 37 pregnancies which followed pyelonephritis, there was but 1 patient in whom there were toxemic symptoms, which developed in a patient who previously had not had toxemia. This fact seems to add weight to the point of view that toxemia and pyelonephritis are separate entities for the most part, with the possibility of occurrence of both in the same pregnancy, but with little else to link them together.

There is little evidence to indicate that the severity of the initial pyelonephritis is any criterion of the persistence of the infection beyond the average rate of spontaneous clearance. Of the mild cases, 5 of 14 patients were still infected at the time of final accounting. Of the moderately severe cases, 3 of 12 patients were known to have remained infected. Six of 19 patients with severe pyelonephritis were

known to have remained infected. In 5 patients, cystocele could have been a factor in retention of infection. In one of these, no upper urinary infection was shown.

Another point of view must be considered. It is generally accepted that pregnancy stasis is primary to pyelonephritis in pregnancy. In those cases in which, through ureteritis and subsequent scarring, hydroureter and hydronephrosis develop, reinfection could easily develop. In one patient in whom such a condition had taken place, reinfection has occurred three times in two years, after clearing of the infected urine had been accomplished by use of sulfanilamide. The urine was sterile to culture when tested at least a week after the withdrawal of the drug in each instance and remained clear for several months. This case is not one of the series. These residual infections are not more resistant to antiseptics than other lesions of the urinary tract unassociated with pregnancy.

Albuminuria.—Abnormal urines are the exception in these cases, if one excepts bacteriuria. In the one toxemic patient who is included in this series, there was found to be definite albuminuria with casts. There was no albuminuria in the 14 mild cases of pyelonephritis at the time of the re-examination. Albuminuria was found in one of the patients who had been classed as moderately severe infections, but in the group which had been classed as severe, 6 of the 15 patients studied showed albuminuria. Casts were not found in any of the pyelonephritis patients except the one who was toxemic in addition to pyelonephritic.

Pyuria.—In any consideration of urinary infection, two classifications of cases have always been made; i.e., bacteriurias and pyurias. The significance of these classes is not great. It is well recognized that the chronic stage of urinary infection is more nearly a bacteriuria and the still active stage of an infection is a pyuria. Often there is the difference of only a few hours between the two conditions in the same patient. At a given time, the determination of the amount of pus present is of some significance in determining the state of the infection, although this cannot be considered to represent constant findings at all times in the given patient. In quiescent infections, there are usually a few pus cells to be noted. We have here considered that 3 to 5 white cells to the high dry microscope lens field were average findings in quiescent infections. Where more cells than that were encountered, it was likely that the infectious process was still active. In the mild infections, there was 1 of the 14 patients who showed pus cells in excess of 3 to 5 per high power field. In the moderately severe cases, 2 of 9 patients examined showed pus, and in those who had been severe, 4 of 16 patients showed pus.

Total Renal Deficiency in Unilateral Infections.—Thirty-one of the 45 patients studied had cystoscopic study at the time of the initial pyelonephritis. Unless there had been extensive studies, including cultures taken under adequate precautions, made at the time of the original pyelonephritis, one could not say with certainty that some of these cases were unilateral. In some, the unilateral nature of the original infection was established, but in many it was not. In the other patients, however, there was absence of symptoms, clear ureteral urines, absence of bacteria on stained preparations from the ureteral catheter urines, and absence of pus. If infection of the supposedly normal other side took place through cystoscopy, it produced no symptoms. Six of the 12 patients with mild cases were cystoscoped, 10 with moderately severe cases, and, as one would expect in that stage of management of pyelonephritis patients previous to present antisepsis, 15 of 19 patients with severe cases were cystoscoped. There were 11 unilateral infections. One of these was a congenital absence of one kidney, and one had insufficient data to establish its nature. Of the 11 patients, 4 were entirely normal to all tests at the time of this study. Seven showed renal

deficiency in some or all of the tests performed. It is of interest, furthermore, that it seemed to make little difference whether one or both kidneys were involved in the initial pyelonephritis for classification of the cases as mild, moderately severe, or severe cases. It was noteworthy, also, that it was of little significance whether there had been unilateral or bilateral initial infection, since total renal deficiency was encountered in both instances. There were no data except the history of the patients to indicate whether infections subsequent to the original pyelonephritis had intervened. History of such occurrence was seldom encountered. In this respect one should note Volhard's[4] statement that excretion of indigo carmine by one healthy kidney may be severely impaired by some reflex action or toxic substance from the diseased opposite kidney and may be found normal after surgical removal of the diseased kidney. There are a few clinical reports in urologic literature of such occurrences. One of us (E. G. C.) has one instance of this condition which occurred in a man; accompanied by high nonprotein nitrogen retention, which continued to rise several days after nephrectomy was done, eventually returned to normal findings, but later became abnormal again after some months.

Phenolsulfonephthalein Test.—Abnormal delay in excretion of phenolsulphonephthalein with ability to concentrate the urine was the most constant abnormality encountered in these cases The total output of the drug was seldom lower than normal. There was a constant finding in most cases that the first fifteen-minute

TABLE I

PHENOLSULFONEPHTHALEIN					NONPROTEIN NITROGEN	CONCENTRATION
15″	30″	45″	60″	TOTAL PER CENT		
26	16	15	7	64	29	1.020
0	14	28	22	64	31	1.028
33	18	10	12	73	32	1.014
10	13	9	7	39	40	1.016
30	22	25	15	92	30	1.017
15	25	12	10	62	25	1.020
18	12	12	6	48	27	1.017
18	18	10	5	51		1.015
1	35	16	9	61	26	1.023
10	20	30	10	70	25	1.023
35	23	13	7	78	35	1.023
25	17	25	10	77	29	1.017
13	20	28	23	84	27	1.016
25	14	18	15	73	26	1.018
27	18	10	10	65	31	1.022
10	15	35	10	70	30	1.020
30	23	10	5	68	25	1.021
20	30	25	8	83	30	1.020
38	32	12	10	92	28	1.025
30	20	17	10	77	28	1.027
40	23	13	6	82	33	1.026
40	17	13	9	79	28	1.018
40	30	10	8	88	33	1.021
50	25	10	7	92	29	1.023
30	18	15	7	71	28	1.026
16	25	38	7	86	28	1.026
14	32	23	10	79	28	1.026
15	28	20	8	71	33	1.022
25	25	20	15	85	36	1.022
10	20	25	20	75	33	1.024
14	25	15	17	71	31	1.022
15	23	14	5	57	28	1.018
16	30	20	8	74	31	1.022
18	13	30	15	76		1.012
15	15	10	5	45		

output was below normal, but that the output in subsequent excretion periods was more satisfactory. The result was a flattened curve of excretion for the group as a whole, as shown in Fig. 1. The data for the 37 patients from whom this figure was obtained are appended in the chart with the nonprotein nitrogen test and the concentration of the urine test.

Nonprotein Nitrogen Test.—There was no evidence of retained nitrogen, as indicated by the estimation of nonprotein nitrogen in 34 cases, except in the one eclamptic patient.

Concentration Test.—It was evident from a study of the data on ability of these patients to concentrate their urines to 1.025 or higher that this test was most likely to show deficiency in the severe cases. Of the total 34 patients tested, 27 failed to concentrate to 1.025. In the group of mild cases, 3 patients concentrated to 1.025 or above. Eleven of the 14 patients were under 1.025. In the moderately severe group, 3 of 8 patients tested were below 1.025, but all were above 1.020. In the severe group, 16 of the 17 patients tested were below 1.025. In all three groups, there were but 7 patients in whom the concentration reached 1.025 or above; 15 concentrated to 1.020 or under; and 3 concentrated to 1.015 or under. The lowest figure was in an uninfected, nontoxemic patient, who concentrated to 1.012.

Hypertension.—Blood pressure readings in excess of 150/90 were found to be present in 9 of these patients. Three of the patients were definitely toxemic in addition to the infections. Six of 42 patients with pyelonephritis showed hypertension five to ten years after the initial infection occurred. Three of these hypertensions occurred in the patients with mild cases and 3 of them with severe cases.

In estimating the normal blood pressure readings for any group, one must consider many factors. We have preferred to accept the averages for the age groups for women as established by Weatherby.[5] He assigns a mean systolic pressure for the age group 30 to 39 of 125.83, with probable error plus or minus 0.48, a standard deviation of 19.79 with probable error plus or minus 0.34, and coefficient of variability 15.73. Since the average childbearing age is about 25, these patients should be expected to fall, and do fall, into the age group 30 to 39 years at the time of re-examination.

Intravenous Pyelography.—Twenty-one of the whole group of study cases had intravenous pyelography. The films were examined for evidence (1) of delayed excretion of the dye; (2) of either acquired or pre-existing abnormalities of the conducting channels, pelvis and ureter; (3) of contracture of the cortex; and (4) concretions.

Six of the 21 cases showed prompt filling of the pelves and ureters early within the first fifteen-minute period after injection of the dye. Nine cases showed the best filling at fifteen minutes, and 2 cases showed best filling at thirty minutes after injection of the dye. In 4 cases, there was such poor filling that the outlines of pelves and ureters were never satisfactorily demonstrated during the course of the examination. Two of the latter cases occurred in the mild and 2 in the severe group.

Five patients showed irregular small calices which were suggestive of contracture of the cortex. Four of these were in the mild group and 1 in the severe group. Four patients showed inflammatory changes in the conducting channels. In 1 there was, in addition, a lesion which suggested aberrant vessel which must have antedated the pregnancy injury.

Stone was present in 5 patients. These calculi were all small in the 3 cases which we demonstrated but, in addition, 2 patients had been operated upon elsewhere for renal calculus. This incidence is far above the normal incidence for a stone in women.

CONCLUSIONS

1. In a survey of 45 patients with pyelonephritis associated with pregnancy, evidence was produced through examination by intravenous pyelography, intravenous phenolsulfonephthalein excretion,

concentration of the urine test, and tests for retention of nitrogen, to indicate that a high percentage of patients suffer appreciable damage to their kidneys which is demonstrable at from five to ten years after the infection. For the majority, adequate renal function is present at that time.

2. In the patient in whom there has been both toxemic and pyelonephritic injury, the prognosis is grave. Hypertension was found to be present in all the patients where there had been both toxemic and pyelonephritis (3 cases). Two of the 3 were dead at 5 years after the injury.

3. Six patients with pyelonephritis showed blood pressure readings above 150/90, associated with some evidence of renal deficiency at that stage of the natural history of the disease.

4. Renal injury, as demonstrated in this group, consisted of injury both to the conduction channels, pelvis and ureter, and to the cortex. When there is injury to the conducting channels, the stasis of urine produced by this condition may further injure the cortex, especially when infection is still present. Stone occurred in 5 of the 45 patients studied.

5. Evidence of total renal deficiency was present at the time of examination in some proved unilateral cases. This finding suggested some other injury than bacterial invasion for the second kidney.

6. It is our impression that the pyelonephritis of pregnancy should be looked upon as a progressive disease in many cases. Data have not yet been produced to indicate to what extent it shortens life. Some of the cases which were subnormal may have shown only the original damage and may now be in a stationary state.

7. Sufficient evidence has been produced to indicate that the aim in treatment in pyelonephritis associated with pregnancy should be to minimize the initial injury and clear the infection as soon as possible.

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ERYTHROBLASTOSIS FETALIS*

With a Report of Twenty-Seven Cases

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ERYTHROBLASTOSIS fetalis designates a disease of the blood-forming organs of the newborn and neonatal infant characterized by anemia and by the presence of an excessive number of immature red blood cells in the circulation. The English hematologists view the disease as a primary hemolytic anemia, the immature red cells resulting from accelerated compensatory regeneration. The American concept advanced by Diamond, Blackfan and Baty entertains a primary overgrowth of immature red cells which undergo rapid hemolysis. Generically, the disease embraces hydrops fetalis, icterus gravis neonatorum, and anemia hemolytica neonatorum.

Ballantine collected 70 cases of hydrops fetalis described in the literature between the years 1614 and 1898. Schridde, in 1910, first recognized the pathology in the hematopoietic organs of infants with hydrops. In 1910, Bachan and Comsie emphasized the presence of large numbers of nucleated red cells in the blood, and the persisting hematopoietic foci in the liver and spleen of infants with icterus gravis. Priority for the description of congenital anemia is accredited to Ecklin whose article appeared in 1919. More recently De Lange, Ferguson, Diamond, Blackfan and Baty, and also Hellman and Hertig, have made illuminating contributions.

HYDROPS FETALIS

Fetal erythroblastosis appears once in every 1,200 to 2,000 confinements. In Stander's clinic, it was encountered once in every 4,000 births and was considered the cause of death in 4.5 per cent of all stillborn infants over 1,500 Gm. A recent article by Macklin records two stillborn infants with normal external appearances in whom autopsy revealed erythroblastosis. The actual frequency of the disease may therefore be greater than recorded. An incidence of 1:2,000 is reported for hydrops fetalis by Hellman and Hertig. Between Jan. 1, 1933 and July 1, 1939, 4 cases of hydrops fetalis occurred in 15,334 confinements at the Brooklyn Jewish Hospital, an incidence of 1 in 3,833 deliveries.

The etiology of erythroblastosis is unknown. In hydrops, as in the other clinical types, a definite racial predisposition is emphasized in the literature. Mediterranean people are especially prone to this illness. In our 4 cases of hydrops, however, one mother was an American-born white, one of American colored stock, and two were of Russian-Jewish extraction. A high familial incidence has been shown by Fanconi

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in a study of 22 families in which erythroblastotic children were born. In Hellman and Hertig's series, the disease was repeatedly noted in 7 of 20 families investigated. The first and last children are generally free from the disease or display only mild manifestations. Nulliparas are rarely affected. An average parity of 5.2 is noted by Hellman and Hertig, who also add that when erythroblastosis appears in any form, there is a 50 per cent chance that the succeeding sibling will present hydrops fetalis. Of 4 mothers in our series who delivered infants with hydrops fetalis, 3 previously delivered stillborn children. The average age was 25.2 and the average parity in our series was 2. Two mothers followed in succeeding pregnancies were delivered of normal children (Cases 2 and 3).

Clinically, hydrops fetalis is the most severe form of erythroblastosis. A stillborn infant or death after feeble respiration is the rule. The longest life period recorded is six days. The infant presents a waxy skin with multiple zones of cutaneous hemorrhage. Edema is marked.

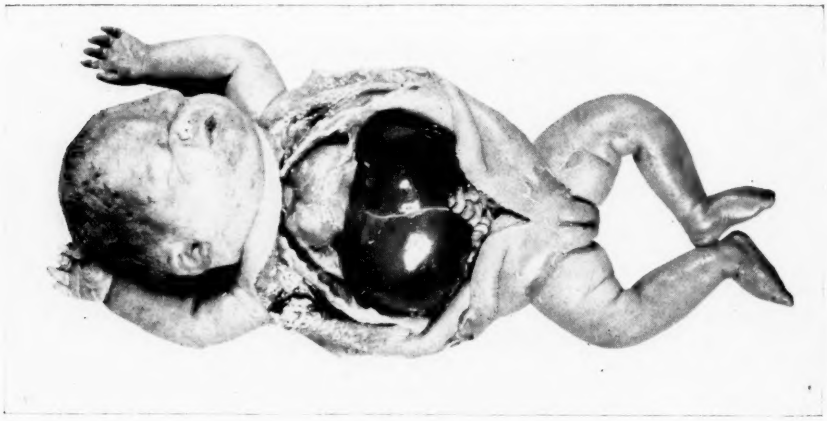

Fig. 1.—Fetus in the hydropic type of erythroblastosis. The superficial tissues are swollen and waxy. Hemorrhagic areas are noted on the face. The huge liver fills the abdominal cavity and contributes to its enlargement.

Jaundice is occasionally noted. The face is enlarged and swollen, the neck short, and the abdomen markedly distended. The latter results from the presence of free fluid in the abdominal cavity and enlargement of the liver and spleen which are felt for varying distances below the costal arch (Fig. 1).

Pathologically, the skin presents marked subcutaneous edema. Petechial hemorrhages are noted in the external and internal organs. The pleural cavity often contains excess fluid. The heart is enlarged, and its weight definitely increased. The abdominal cavity holds a varied quantity of serosanguineous fluid. The liver reaches from two to five times its normal dimensions and is reddish brown and glistening. On cut section its lobular structure is somewhat obscured. Microscopically, zones of toxic necrosis and deposition of iron or bile pigment are encountered. Hematopoiesis is pronounced. The sinusoids are distended and contain numerous premature cells of the red cell series (megaloblasts, erythroblasts, and normoblasts). The white cell group is repre-

sented by the myeloblast and myelocyte (Fig. 2). The portal canals are filled with similar cells. The spleen is enlarged, soft, and reaches four to five times its normal size and weight. It is generally firm in consistency and red brown in color. Malpighian corpuscles are not reproduced. The pulp is filled with hordes of immature nucleated red cells and large progenitors of the white cell series. Pigment-laden phagocytes are numerous. The pancreas, adrenals, kidneys, prostate, thymus and pituitary share in the extramedullary proliferation of immature blood cells. The bone marrow is hyperplastic and compactly filled with proliferating erythroblastic and myeloblastic cells, the former largely predominating. The placental changes are noteworthy. The organ is enlarged, soft, and friable. Its maternal aspect is deeply fissured. The yellow gray color is striking. The fetal placental weight ratio is altered

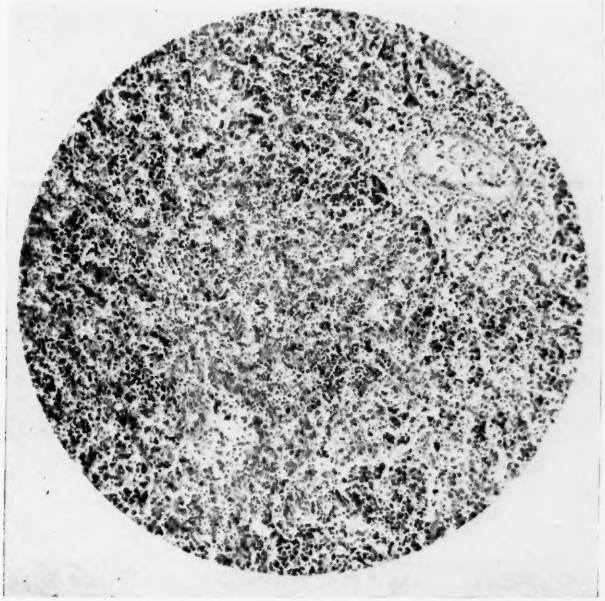

Fig. 2.—Liver in erythroblastosis fetalis. The liver cords are widely separated. The sinusoids are filled with large numbers of immature red blood cells. Immature white cells can also be identified. The portal canals also show persistent hematopoiesis. ×150.

from the normal of 6:1 and can reach an extreme of 3:1. Edema of the organ is the accounting factor. Microscopically, the villi are large and even in premature placentas reach beyond the normal size. The syncytial cells are regularly spaced. Syncytial buds are frequent. The Langhans layer may focally persist. The stroma is edematous but hyperplasia may be pronounced. Hofbauer cells normally present only in the early placenta are encountered with moderate frequency. The capillaries are reduced in number and contain numerous red and white blood cells (Fig. 3).

The hematologic changes in this lesion are diagnostic and will be more fully discussed under icterus gravis. Reduction in the number of red cells is outstanding. The hemoglobin, too, is low but the color

index is above the normal. The number of nucleated cells, which in the neonatal period range from 20 to 25,000, is markedly increased. The rise in the number of nucleated red blood cells is especially pronounced, and normoblasts sharply increase above 15 per cent, the high normal figure for the neonatal period. Erythroblasts, megaloblasts, myeloblasts and myelocytes are found on smear. Studies of the blood picture in hydrops cases, as a rule, are incomplete or entirely omitted because of the early death of the infant. In our series only three infants had partial blood studies, all made post mortem. One showed 78 normoblasts per 100 white blood cells (Case 2). One showed 149 normoblasts for every 50 cells of the white cell group (Case 4). Case 1 studied by post-mortem sternal puncture showed a marked increase in the ratio of early red cells.

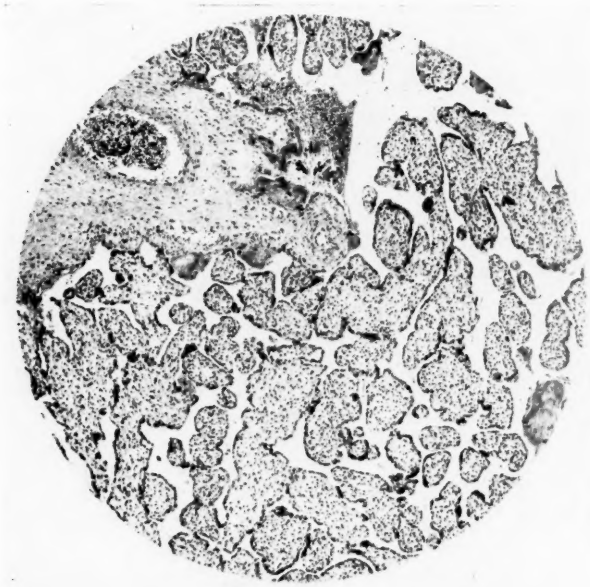

Fig. 3.—Placenta. The large size of the villi is prominent. Note the immature mesenchymal stroma. Hofbauer cells are not infrequent. The syncytium is vesicular. Large numbers of syncytial buds are prominent. Note the large numbers of nucleated red cells in the vein of a main stem villus. ×80.

Pregnancy associated with hydrops fetalis is frequently accompanied by hydramnion. This may explain the increased incidence of premature labor. Of 4 patients, one was delivered in the thirty-fourth week, one in the thirty-sixth week, one in the thirty-seventh week, and one in the thirty-eighth week. The incidence of toxemia of pregnancy is above the normal. In the series reported by Hellman and Hertig, it was encountered in 30 per cent of the patients. In our group, 2 of the 4 patients showed moderate toxemia evidenced by edema, moderate rise of blood pressure and albuminuria. Maternal blood studies are not recorded with sufficient frequency to determine any correlation between fetal and maternal hematopoietic abnormalities.

Labor may be complicated. In 2 of our 4 patients (Cases 3 and 4), fetal dystocia resulted from the enlarged abdomen. In Case 3, it delayed delivery after internal version was performed for prolapse of the cord. Abdominal paracentesis and partial evisceration were necessary to complete the delivery of Case 4. The third stage as a rule follows without incident, in spite of the huge size and weight of the placenta.

The diagnosis of hydrops fetalis is easily established at birth by the clinical appearance of the infant, and confirmed by study of smears made from cord blood. Even before delivery, an amber colored amniotic fluid directs suspicion. Intrauterine diagnosis can be made by x-ray as first shown by Hellman and Irving. In the roentgenogram, the subcutaneous tissues are definitely thickened and show marked density. A corona surrounds the bones of the skull due to marked edema of the scalp. Congenital syphilis must be excluded, for like erythroblastosis it too may affect successive infants causing death in utero or early in the post-partum period. Enlargement of the liver, spleen, and placenta completes the parallel between syphilitic and erythroblastic infants. X-ray studies of the long bones for osteochondritis, microscopic examination of the placenta, serologic examination and smear of the cord blood clarify the situation.

The prognosis of hydrops fetalis is bad. Survival of the infant is practically unknown. Because of the tendency of recurrence in succeeding pregnancies, advisability of future childbearing must be strongly considered. There is no effective treatment. Liver and vitamins have been administered to mothers as prophylactic measures.

CASE REPORTS OF HYDROPS FETALIS

CASE 1.—Mrs. E. B. (No. AA43210), para ii, aged 28 years, Russian Jewess, was admitted Jan. 15, 1938, because of suspected nephritic toxemia. The first preganncy in 1933 was uneventful. The second pregnancy in 1935 resulted in the birth of a premature stillborn infant at 7½ months. The present pregnancy dates from June 25, 1937, and was uneventful until Jan. 11, 1938, when edema and elevation of blood pressure appeared. There was no response to medical treatment. On admission the physical examination was essentially negative. The uterus measured 23 cm. Fetal presentation was L.S.A. and the fetal heart normal. The pelvic measurements were ample. Bilateral edema of the fingers and legs was noted. The blood pressure was 164/76. The urine showed 4-plus albumin with moderate numbers of casts and occasional red blood cells. The Kahn and Wassermann reactions were negative. The blood studies revealed mild secondary anemia. Labor occurred prematurely on Feb. 22, 1938, and resulted in the birth of a stillborn breech infant which weighed 3,300 Gm. The edematous placenta, weighing 1,680 Gm., was delivered spontaneously five minutes later. The post-partum course was uneventful. Autopsy revealed a female infant 41 cm. in length and weighing approximately 3,178 Gm. The skin was edematous and contained numerous zones of hemorrhage. The abdomen was especially protuberant and measured 40 cm. in circumference. Upon incision 600 c.c. of clear straw-colored fluid was evacuated. The lungs were collapsed. The heart was enlarged and measured 4 cm. from apex to base and 4 cm. transversely across the base. The weight was 22 Gm. The atria were dilated. The valves, chordae tendinae, papillary muscles, and ventricular walls showed no abnormalities. The ductus arteriosus and the foramen ovale were patent. The gastrointestinal tract presented no pertinent findings. The liver reached 6 cm. below the costal arch and the dome of the diaphragm was definitely elevated. It measured 13 by 9 by 4 cm. and weighed 183 Gm. (normal 78 Gm.). The external surface was smooth,

shiny and red brown. On cut section the markings were indistinct. Microscopically, the arrangement of the lobules was fairly well preserved. The central veins, however, were dilated and contained numerous nucleated red blood cells. The dilated sinusoids were compactly filled with huge numbers of early red and white cells. The portal canals similarly contained young white and red blood derivatives. The pancreas was normal. The suprarenal glands presented no abnormalities but the medullary segments contained foci of hematopoiesis. The blood vessels were crowded with normoblasts, megaloblasts, and myeloblasts. Similar areas of hematopoiesis were noted in the cortical and medullary segments of the kidneys. The genitalia were normal. The spleen was enlarged and weighed 32 Gm. (normal 8 Gm.). It measured 7 by 5 by 4.2 cm. The external surface was smooth, the color brown purple. On cut section the Malpighian corpuscles were indistinct. Microscopically, the sinusoids and the pulp were crowded with huge numbers of early red and white cells. The bone marrow as studied in the ribs, vertebras, and tibia showed marked hyperplasia and the

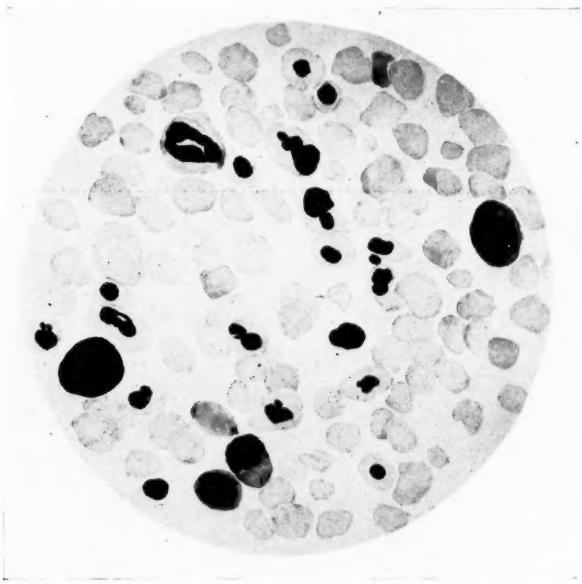

Fig. 4.—Photographed drawing of smear from sternal bone marrow puncture. Note the erythroblasts in the upper portion. Normoblasts are numerous. The large, deeply-staining, round cells are megaloblasts.

marrow spaces were packed with nucleated red cells, early white cells, and occasional megakaryocytes. A post-mortem sternal puncture showed a ratio of 5 white cells to 95 erythroblasts (normal ratio 95:15; Fig. 4). The ratio of early red cells to matured red cells was 40:60 (normal ratio 15:85). The cranial cavity showed clotted blood in the middle and posterior fossae. The falx and tentorium were normal. The brain weighed 182 Gm. and presented no abnormalities. The edematous placenta weighed 1,680 Gm. and measured 24 by 13 by 3 cm. The maternal aspect was deeply fissured. Microscopically, the chorionic villi were larger than normal and the syncytial cells were somewhat flattened. Langhans' cells were focally retained. The connective tissue stroma was vacuolated and Hofbauer cells encountered with moderate frequency. Syncytial giant cells were numerous.

Case 2.—Mrs. E. G. (No. AA29066), primipara, aged 23 years, American-born, was admitted in labor Oct. 6, 1933. The last menstrual period occurred Jan. 11, 1933, and the estimated date of confinement was Oct. 18, 1933. Labor terminated prematurely at the thirty-seventh week. The child lived only forty-five minutes.

Autopsy revealed a female infant with striking subcutaneous edema of the skin and mucous membranes. The abdomen was distended. The peritoneum and pleural cavities contained an excessive amount of straw-colored fluid. The heart weighed 20 Gm.; the myocardium was pale and edematous. The liver weighed 115 Gm. and was red, smooth, and glistening. Microscopic examination revealed numerous islands of hematopoiesis in the sinusoids and in the portal canals. The spleen was enlarged and weighed 33 Gm. Its surface was smooth and red. Microscopic examination revealed the stroma and sinusoids filled with numerous immature cells, many of which were megaloblasts. There were foci of hematopoiesis in the skin, intestine, kidney, uterus, pancreas, and adrenals. The ribs and long bones contained a deep red marrow which showed marked erythroblastic activity. The post-mortem blood smear revealed 78 normoblasts per 100 white cells and 17 megaloblasts per 100 white cells. The differential count revealed 69 per cent lymphocytes, 14 per cent polymorphonuclear cells, 6 per cent band forms, 3 per cent eosinophiles, and 7 per cent myeloblasts. The placenta was not studied. A subsequent confinement on Dec. 8, 1937 resulted in the birth of a normal, full-term male infant which weighed 3,486 Gm.

CASE 3.—Mrs. R. S. (No. AA2453), para i, aged 26 years, Russian Jewess, was admitted in labor Oct. 7, 1934. The first pregnancy in 1932 terminated in the birth of a full-term stillborn infant. The last menstrual period occurred Jan. 18, 1934, and the estimated date of confinement was Oct. 25, 1934. On admission there was slight edema of the extremities and polyhydramnion. With full dilatation, artificial rupture of the membranes was followed by the prolapse of the cord. Delay in delivery of the child after podalic version was due to the enlarged abdomen and resulted in a stillborn male infant, weighing 4,131 Gm. The edematous placenta followed spontaneously. At autopsy, the skin was markedly edematous, the abdomen greatly distended, containing 300 c.c. of amber-colored fluid. Each of the pleural cavities contained 75 c.c. of yellowish red liquid. The heart was enlarged, weighed 30 Gm. and showed dilatation of the atria. The lungs were collapsed. The liver weighed 159 Gm., the surface was smooth and the consistency firm. The spleen was also enlarged, weighing 30 Gm. and was covered by a fibrinous exudate. Microscopic examination of the organs showed numerous areas of hematopoiesis in the liver, spleen, kidneys, and adrenals. The placenta weighed 1,930 Gm. and presented the classical pale, soft, fissured appearance. The villi showed marked edema, and the capillaries were filled with numerous nucleated red blood cells. The succeeding confinement in December, 1936, resulted in the birth of a normal, full-term male child, weighing 3,968 Gm.

CASE 4.—Mrs. J. B. (No. 209438), para ii, colored, born in the United States, was admitted in labor on Feb. 17, 1938. The first pregnancy in 1936 resulted in a stillborn infant at seven and one-half months. The last menstrual period occurred July 1, 1937, and the estimated date of confinement was April 8, 1938. The Wassermann test was positive and the patient received eight injections of salvarsan during her ante-partum course. On admission the blood pressure was elevated to 150/98. Fetal dystocia resulted from the markedly enlarged abdomen. Paracentesis, accordingly performed, was followed by a large gush of fluid, after which the dead male infant was easily delivered. The placenta followed spontaneously. The smear from the cord blood immediately studied showed 149 normoblasts for every 50 white blood cells. Autopsy revealed a colored male child 43 cm. in length and weighing 2,050 Gm. The heart weighed 15 Gm. and was otherwise normal. The liver weighed 78 Gm. (enlarged for premature). Its surface was smooth, glistening, and deep red. Microscopic examination revealed numerous foci of hematopoiesis. The central veins, sinusoids, and portal canals were filled with numerous normoblasts and megaloblasts. There were no miliary gummas and spirochetes were not demonstrated. The spleen, kidneys, and adrenals showed numerous zones of hematopoiesis. The bone marrow was packed with immature red and white cells. The soft friable placenta weighed 915 Gm. (ratio 2:1). Microscopic examination revealed enlarged chorionic villi with vacuolated stroma and occasional Hofbauer cells. The fetal veins and capillaries contained large numbers of normoblasts and occasional erythroblasts and myeloblasts.

ICTERUS GRAVIS NEONATORUM

Icterus gravis neonatorum designates that clinical form of erythroblastosis, in which jaundice is the most prominent symptom. Edema is supposedly lacking, but in our series are included five infants presenting circumscribed swelling of the subcutaneous tissues. As will be noted below, these cases were severe and clinically are perhaps considered as intermediary between hydrops and icterus gravis.

Icterus gravis is not infrequent. Hellman and Hertig report an incidence of 1 in every 1,500 confinements. In our survey from Jan. 1, 1933, to July 1, 1939, 20 cases of icterus neonatorum were encountered in 15,334 deliveries, an incidence of 1 in every 767 confinements. The etiology is unknown. Mediterranean ancestry is emphasized as a predisposing cause, but in our series of 19 mothers who delivered 20 icteric infants, 12 were born in the United States, 2 in Austria, 2 in Russia, 1 in Germany, 1 in Italy, and 1 in Rumania. There were no patients of the colored race. Multiparas predominate and in our series the average parity was 2.7; the average age was 31.2 years. Recurrence of the disease in succeeding pregnancies is frequent. Hellman and Hertig indicate that once erythroblastosis has appeared there is an 80.3 per cent chance that the succeeding child will present icterus gravis. Of our 19 mothers, 4 delivered stillborn infants in earlier pregnancies. Four others had previous erythroblastotic children. Infants 1 and 2 were succeeding icteric children from the same mother. In Case 3, hydrops fetalis and 3 other stillbirths anteceded the birth of the icteric infant. In Case 6, the second infant presented congenital anemia and the third, icterus gravis. In Case 18, the first pregnancy was a full-term stillbirth; the second child succumbed to icterus gravis. The third and fourth pregnancies of this mother terminated in premature stillborn children at six and eight months, respectively. Two mothers who delivered icteric children were followed in succeeding pregnancies. The mother of Case 1 delivered a second icteric child. In Case 20, the succeeding pregnancy terminated in a premature stillborn infant, evidently due to strangulation of the cord.

The most prominent symptom of icterus gravis is jaundice which may be present at birth or be delayed for twenty-four to forty-eight hours after delivery. A saffron yellow vernix caseosa arouses suspicion. In our series 6 infants were jaundiced at birth. In 5, icterus appeared within eight hours; in 5, between eight and twenty-four hours; and in the remaining 6, within twenty-four to forty-eight hours after delivery. The infants are generally listless, apathetic and feed poorly. As the disease progresses, stupor and convulsions appear. In the terminal stages, vomiting, dyspnea, cyanosis, and frothing of blood-stained fluid are frequent manifestations. Cutaneous hemorrhage is not uncommon. Though jaundice may be intense, the mucous membranes are not uncommonly pallid. Enlargement of the liver and spleen affords palpation of these organs for varying distances below the costal margin.

The pathologic changes are essentially similar to those encountered in hydrops. Diffuse edema, however, is lacking although circumscribed swelling was noted in five infants. The skin, as the other fetal tissues, presents icterus of varying degree. The heart is enlarged and its chambers dilated. The size, however, is somewhat smaller than noted in hydrops. The peritoneal cavity contains small amounts of fluid. The liver is increased two to five times its normal dimensions. The weight is augmented. The color is greenish brown. On cut section the sinusoidal markings are poorly defined. Microscopically, the dilated sinusoids are compactly filled with nucleated red cells and the early large progenitors of the white cell group. Numerous foci of hematopoiesis are present. The liver cords are compressed and the liver cells contain bile pigment and hemosiderin. The portal canals show persistent hematopoiesis. The spleen is similarly enlarged from two to five times its normal dimension and generally presents a purple red color. The Malpighian corpuscles are not reproduced. The pulp shows numerous foci of erythropoiesis. Pigment laden endothelial phagocytes are frequent. Other organs, too, show extramedullary blood formation but seemingly with less fre-

quency than in the hydrops group. The bone marrow is hyperplastic and is compactly filled with huge numbers of early red blood cells. The brain may present a striking appearance. The basal ganglia (thalamus, corpus striatum, caudate nucleus, olivary bodies, vermis, and the floor of the fourth ventricle) take a yellow, yellow green, or olive stain; so-called "Kern-icterus." Microscopically, the brain cells in these areas contain yellow pigment granules in the body cytoplasm. This was encountered at autopsy in four cases (7, 12, 16, 19). The placenta is generally normal in its gross appearance. Microscopically, there are a few departures from the normal. The Langhans layer is occasionally retained. Hofbauer cells are noted. The diagnosis, however, is generally established by the finding of excessive numbers of nucleated red blood cells in the capillaries of the villi.

The hematologic findings reveal a hyperchromic anemia. The red cells average 3.4 million compared to a normal of 5.2 to 5.6 million for the neonatal period. The hemoglobin is reduced and averages about 51 per cent. The color index is high. Nucleated cells range from 23,000 to 256,000. The normal is 20,000 to 25,000 for this period. Fifty per cent to 90 per cent of the nucleated cells belong to the red cell type, contrasting with the average normal of 5 to 15 per cent for the neonatal period. The bleeding time is prolonged, the clotting time is normal. The icteric index is markedly elevated. Fragility of the red blood cells shows no departure from the normal. In our series the hemoglobin varied from 50 to 160 per cent. The red blood cells ranged from 1.43 to 6.75 million per c.mm. Polycythemia occurred in 4 cases (1, 4, 8, 11). Nucleated red cells varied from 7 to 300 per cent with an average of 69 per cent.

Pregnancy associated with icterus gravis shows a greater incidence of toxemia. Hellman and Hertig report two mild cases in 19 mothers. Mild toxemia was observed in Cases 1, 4, 5, and 8 of our series. Labor, as a rule, is frequently premature. Nine of our 20 infants were delivered prematurely; 2 in the thirty-fourth week, 1 in the thirty-fifth week, 3 in the thirty-sixth week, 1 in the thirty-seventh week, and 2 in the thirty-eighth week. Labor was of normal duration and averaged 11.3 hours for our series. The weight of the children ranged from 2,300 to 3,996 Gm. The average weight was 2,948 Gm. Blood studies on mothers were not made with sufficient frequency to warrant any statement.

The diagnosis of icterus gravis is easily made. Jaundice, an enlarged liver and spleen and an increased number of nucleated red cells form a diagnostic triad. A golden yellow vernix if present at birth is indicative of the illness. Icterus gravis should be anticipated in a mother presenting a history of repeatedly stillborn infants without apparent cause or where a history of previous erythroblastosis is obtained.

The illness is grave and the fetal mortality as reported in the literature reaches from 50 to 80 per cent. Infants with icterus at birth receiving prompt and adequate treatment show a better prognosis. Of 7 infants with icterus at birth, 3 were recognized and prompt treatment resulted in recovery. Three others died without therapy because the lesion was not diagnosed. The fourth infant succumbed in spite of transfusion because of concomitant cerebral hemorrhage. Of 7 in whom jaundice appeared within twenty-four hours, 1 recovered and 6 died. Of the remaining 6 infants displaying icterus between twenty-four and forty-eight hours after birth, 5 succumbed. Six of the fatal cases presented 85 per cent or more normoblasts on examination of the blood smear. Of these, 1 died in fifteen hours, 3 within thirty-one hours, 1 in sixty hours, and 1 in sixty-six hours. Cases with circumscribed edema were severe and in our series all died. Recovery may be followed by a phase of anemia. Cirrhosis of the liver and neurologic lesions are on record as sequelae.

As in the therapy of hydrops fetalis, liver, iron, and vitamins have been advised as prophylactic measures for mothers who have previously delivered erythroblastotic children. Treatment of the icteric infant should be prompt and immediate for the prognosis frequently depends upon early and adequate measures. Intramuscular injections of human blood serum or whole blood have been employed with varying results. Five to 15 c.c. of serum are administered daily for a total of 30 to 60 c.c. Hampson reports 17 recoveries in a group of 18 icteric infants

TABLE I. MATERNAL FINDINGS IN ICTERUS GRAVIS

CASE	AGE	PARITY	NATIONALITY	PREVIOUS STILLBIRTHS CAUSE UNKNOWN	PREVIOUS ERYTHROBLASTOSIS	MILD TOXEMIA	LABOR			POST PARTUM	SUBSEQUENT PREGNANCIES
							WEEK	DURATION (HR.)	TERMINATION		
1	27	i	Am.-Jewess	0	0	+	36	8	Spont.	Normal	Erythroblastosis
2	28	ii	Am.-Jewess		1—Icterus gravis	0	40	3	Spont.	Normal	
3	38	vii	Aust.-Jewess	3	1—Hydrops fetalis	0	35	3	Spont.	Normal	
4	42	vi	Aust.-Jewess	0	0	+	37	33	Spont.	Normal	
5	26	ii	Am.-Jewess	0	0	+	36	3	Spont.	Normal	
6	22	iii	Am.-Jewess	0	1—Cong. anemia, recovered	0	40		Spont.	Normal	
7	24	ii	Am.-Italian	1	0	0	40		Cesarean section	Normal	
8	36	iii	Rum.-Jewess	0	0	+	40	14	Spont.	Normal	
9	29	ii	Am.-Jewess	0	0	0	40	12	Spont.	Normal	
10	38	iv	Am.-Jewess	0	0	0	38	8	Version, breech extraction	Normal	
11	33	iv	Am.	0	0	0	40	10	Spont.	Normal	
12	32	ii	Am.-Jewess	0	0	0	36	2	Spont.	Normal	
13	27	i	Russ.-Jewess	0	0	0	34	4	Spont.	Normal	
14	35	ii	Am.	1	0	0	38	8	Low forceps	Normal	
15	38	ii	German	0	0	0	40	14	Spont.	Normal	
16	28	ii	Am.-Jewess	0	0	0	40	22	Spont.	Normal	
17	23	ii	American	0	0	0	40	9	Spont.	Normal	
18	38	v	Russ.-Jewess	3	1—Icterus gravis	0	39	15	Spont.	Normal	
19	26	i	Am.-Jewess	0	0	0	34	30	Spont.	Normal	
20	30	ii	Am.-Jewess	0	0	0	39	6	Spont.	Normal	Stillbirth

treated by this technique. The series reported by Hawksley and Lightwood, in 1934, however, shows unsatisfactory results with this method. Blood transfusion is the treatment of choice. Fifty to 75 c.c. of blood should be given at once and repeated as often as necessary to maintain constancy in the number of the red blood corpuscles and an ample level of hemoglobin. In Case 8 which recovered, polycythemia indicated the phlebotomy employed prior to the two transfusions administered. Blood by continuous intravenous infusion seems indicated when intensive jaundice is associated with a rapidly falling hemoglobin. In our series, 3 babies received no blood in any form or manner, and all died (Cases 11, 12, and 19). Two infants received a single injection of 20 to 30 c.c. of whole blood,

TABLE II. FINDINGS IN NEWBORN INFANTS WITH ICTERUS GRAVIS

CASE	SEX	BIRTH WT. (GM.)	ONSET OF JAUNDICE (HR.)	LIVER	SPLEEN	BLOOD STUDY				THERAPY			RESULT		COMMENTS
						HB. %	R.B.C. (M.)	NUC. CELLS	NUC. R.B.C. %	ONSET AFTER BIRTH (HR.)	SERUM	TRANSFUSION	DIED (HR. AFTER BIRTH)	RECOVERED	
1	M	2,610	48			160	6.75	32,800	21	72		65 c.c.	120		
2	F	3,150	Birth	1 F*	0	107	4.50	33,200	16	Birth	50 c.c.			+	
3	M	2,460	4	4 F	4 F	70	3.00	30,000	300	8		50 c.c.	15		Edema of scrotum and extremities, severe type
4	M	3,996	24	1 F	1 F		6.50	19,800	41	24		60 c.c. + 30 c.c. whole blood	36		Autopsy refused
5	F	2,578	6	2 F	2 F	52	1.46	12,800	85	8		480 c.c.	28		Adequate therapy; cerebral hemorrhage
6	F		3 Home delivery	2 F	2 F	50	2.35	44,800	58	8		800 c.c.		+	Ict. index -400; sec. anemia after 4 mo.
7	M	3,290	24	2 F	2 F	70	3.80	64,800	Innum.	26		70 c.c.	31		
8		2,940	Birth—yellow vernix	2 F		150	6.50	28,000	30	Birth		100 c.c.		+	Phlebotomy of 25-40 c.c. blood before each 50 c.c. transfusion
9	M	3,716	48		2 F	100	3.90	46,200	48	48		75 c.c.		+	
10	M	2,752	48	1 F	1 F	110	3.50		7	72		60 c.c.	76		Died shortly after transfusion—reaction?
11	M	3,632	Birth—yellow vernix	2 F	2 F	98	5.90	43,750	53	None			17		
12	M	2,550	48	1½ F	1½ F	94	4.50	5,650	0	None			74		
13	F	2,298	Birth				3.00		Innum.	28		20 c.c. whole blood	31		
14	F	3,060	Birth	1 F	1 F	50	3.10	12,000	143	8		200 c.c.	66		Adequate therapy; cerebral hemorrhage
15	F	3,060	12	2½ F	1 F	100	1.43	29,450	90	30		280 c.c.		+	
16	F	2,780	24	1 F	1 F	80	2.90	32,500	22	24		60 c.c.	84		Therapy when child in extremis
17	M	3,088	9			70	4.70	14,500	59	14		60 c.c.	24		Autopsy refused
18	F	2,948	Birth							Birth		20 c.c. whole blood	11		Not recognized clinically.
19	F	2,550	36							None			72		No blood studies
20	F	3,088	48			50	1.78	117,600	Innum.	48	50 c.c.		60		Autopsy refused

*F, Fingers below costal margin.

TABLE III. PATHOLOGIC FINDINGS IN ICTERUS GRAVIS

CASE	LENGTH (CM.)	WT. (GM.)	EDEMA	LIVER		SPLEEN		HEART	OTHER ORGANS WITH ERYTHROPOIESIS					CEREBRAL HEMORRHAGE	KERN-ICTERUS	PLACENTA		OTHER FINDINGS
				WT.—NORMAL †78 GM.	ERYTHROPOIESIS	WT.—NORMAL †8 GM.	ERYTHROPOIESIS	WT.—NORMAL †17 GM.	BONE MARROW	PANCREAS	KIDNEYS	ADRENALS	OTHERS			GROSS	MICRO.	
1	44	2,280	0	100	+	12	+	12	+	+				+ Between galea and epicranium	0	Normal	*	
3	44	2,340	Scrotum, lower extremities	162	+	40	+	21	+	+	+			0	0	Normal	*	
5	48	3,500	Scrotum, peritoneal cavity, 50 c.c.	170	+	32	+	30	+			+		+	0	Normal	*	
														Lateral ventricle and cisterna basalis	0	Normal	*	
7	53	3,450	Face, extremities	185	+	50	+	15	+	+	+			0	+	Wt. 700 gm.	Nuc. R.B.C. in vessels	

10	45	2,450	0	144	+	20	+	17	+	+				0	0	Normal	*	Patent foramen ovale and ductus arteriosus
11	47	3,700	0	102	+	10	+	32	+	+	+			0	0		Nuc. R.B.C. in vessels	
12	46	2,900	0	110	+	15	+	15	+			+	Lymph nodes	0	+	Normal	*	
13	45		Peritoneal cavity, 20 c.c. Pleural cavity, 20 c.c.	80	+	20	+		+	+				0	0	Normal	*	Atresia of hepatic duct
14			Subcutaneous	160	+	30	+	25				+		+ Upper surface of cerebellum	0	Normal	*	Atelectasis of lungs
16	48	2,790	0	105	+	14	+	12	+		+			0	+	Normal	*	
18			0	220	+	38	+	30	+		+			0	0	Normal	*	Post mortem blood. Innumerable normoblasts
19	47		Peritoneal cavity, 20 c.c.	128	+	12	+	17	+		+	+	Thymus	0	+		*	Patent foramen ovale and ductus arteriosus

*Placenta not saved for microscopic examination.
†Normal weights of liver, spleen, heart for full-term newborn.

and 2 received 50 c.c. of serum intramuscularly. Only 1 survived (Case 2). Of the remaining 13 infants, 11 received transfusions alone. One received a transfusion of 65 c.c. followed by continuous transfusion. In 1, intramuscular injection of whole blood preceded transfusion. There were 9 deaths in this group of 13 infants, a mortality of 69 per cent. One infant (Case 10) died as a result of a reaction following transfusion, although the patent ductus arteriosus and foramen ovale found upon autopsy may have been auxiliary causes. In Case 5, advanced cerebral hemorrhage with compression of the midbrain precluded recovery. Case 14 showed cerebellar hemorrhage and pulmonary atelectasis. In these 3 infants, recovery could not be expected. In the remaining 6 cases, of which 4 were severe and 2 mild, adequate blood was administered by repeated transfusions. In the entire series of 20 infants only 5 survived, a mortality of 75 per cent. The five infants who recovered received prompt and repeated transfusions. The important maternal, fetal, and pathologic data of 20 cases of icterus gravis are summarized in Tables I, II, and III.

ANEMIA HEMOLYTICA NEONATORUM

Anemia hemolytica neonatorum represents that form of erythroblastosis in which pallor of the skin and mucous membranes is the most pronounced feature. It may be the healed phase of icterus gravis (Case 6, Icterus). As in hydrops and icterus gravis, the liver and spleen are enlarged and an increased number of normoblasts appears in the peripheral circulation. Edema is lacking.

The incidence of anemia neonatorum is difficult to ascertain. Mild cases may go unrecognized, or are considered as physiologic icterus, for mild jaundice often precedes anemia. In 15,334 deliveries, from Jan. 1, 1933, to July 1, 1939, only 3 cases were encountered, an incidence of 1 in 5,111 confinements. The mothers were all born in the United States. The parity was 2.6 and the average age 28 years. Case 3 was from a twin pregnancy. Its mate succumbed to icterus (Case 12, Icteric series). Case 2 in the anemia group was followed by a sibling with icterus gravis (Case 6).

The outstanding characteristic of congenital anemia is pallor of the skin and mucous membranes. Though this feature is apparent at birth it is generally obscured by jaundice. With recession of icterus, whiteness of the skin becomes pronounced. Pallor of the mucous membranes is noteworthy. In our series, pallor appeared within forty-eight hours in Case 1. In Case 3, however, it was not apparent until the seventh day, and in Case 2, was not manifest until the tenth day after birth. Antecedent icterus was present in each instance but was only of mild degree. The infants are listless, weak, and nurse poorly. Enlargement of the liver or spleen or both is noted, but generally to a lesser degree than observed in icterus gravis or hydrops. It was found in all our cases. There is no edema. Petechial hemorrhages of the skin are noted in the literature but were not present in our group.

As in other forms of erythroblastosis, persisting hematopoiesis in the liver and spleen is classical. The degree, however, is not as advanced as in hydrops or icterus. Extramedullary blood formation in other organs may be present. The bone marrow is hyperplastic. The placenta is grossly normal. The hematologic findings are essentially similar to those of icterus gravis. The number of nucleated red cells in the peripheral blood is reduced although still remaining above the normal. The hemoglobin ranged from 18 per cent to 53 per cent and the red cells from 850,000 to 2,600,000. Case 2 showed 45 per cent normoblasts on smear. In Case 3, normoblasts numbered 1 per cent on the third day. Myelocytes were found in Case 2.

The diagnosis of anemia neonatorum is easily established by the pallor, enlargement of the liver or spleen or both and the characteristic blood picture. The prognosis is good, but the disease may run a prolonged course. Diamond,

Blackfan and Baty indicate that the anemia may remain stationary or even become aggravated until the sixth week of life. At this time there is a return of a normal number of young erythrocytes. Finally, the hemoglobin and red cells increase to the normal though a 4-month interval may be required for complete restoration. Repeated small transfusions of 50 to 75 c.c. of citrated blood are the specific treatment. The amount employed, however, is varied in each instance depending upon the maintenance of an adequate number of red cells and a high hemoglobin level in the blood. Liver and iron in sufficient doses are important aids in the recovery.

CASE REPORTS OF ANEMIA HEMOLYTICA NEONATORUM

CASE 1.—Mrs. Y. C. (No. 173116), para iii, aged 31 years, American born, was admitted in labor Sept. 1, 1935. The first pregnancy in 1923 resulted in a spontaneous abortion at two and one-half months. The second pregnancy in 1924 and the third pregnancy in 1928 were uncomplicated. The last menses occurred on Nov. 20, 1933, and the estimated date of confinement was Aug. 27, 1934. Labor terminated by low forceps after twenty-three hours, resulted in the birth of an apparently normal female infant, weighing 3,360 Gm. Slight jaundice was first observed forty-eight hours after birth. There was definite pallor of the mucous membranes. The spleen reached 3 cm. below the costal margin. The liver was not felt. The blood study showed 1.8 million red cells and 32 per cent hemoglobin. Smears were not made. On the fourth day after birth, a direct transfusion of 75 c.c. of blood was administered. The child was definitely improved and nursed more vigorously. A second transfusion of 75 c.c. was administered on September 7 (the sixth day of life). On discharge from the hospital September 9, the hemoglobin was elevated to 70 per cent and the red cells numbered 2.9 million per cm. The placenta which weighed 440 Gm. showed no gross or microscopic abnormalities.

CASE 2.—Mrs. F. C. (No. AA34709), para i, aged 21 years, American born, was admitted April 2, 1935, immediately following her home delivery. The first pregnancy in 1934 terminated normally. The last menses occurred July 14, 1934, and the estimated date of confinement was April 30, 1935. Labor occurred on April 2, 1935 (thirty-sixth week) and terminated spontaneously in the birth of a female infant weighing 2,640 Gm. On the tenth day after birth, the infant presented marked pallor and slight icterus. It nursed poorly. The liver and spleen were found enlarged, and the latter reached the level of the umbilicus. A blood study revealed 1.35 million red cells and 50 per cent hemoglobin. Nucleated cells numbered 30,000. Upon differential smear 45 normoblasts were noted per 100 white cells. There were 41 per cent neutrophiles, 31 per cent lymphocytes, 10 per cent myelocytes, and 11 per cent metamyelocytes. The child received a transfusion of 75 c.c. of citrated blood and several injections of liver extract. This was followed by marked improvement. Anemia, however, persisted and on April 15, thirteen days after delivery, the hemoglobin was only 35 per cent and the red cells 1.5 million. The use of liver extract was continued after the child was discharged from the hospital. Complete recovery ultimately followed.

CASE 3.—Baby A of twin pregnancy (see Case 12 of icteric group). Its mate, Baby B, died of icterus gravis seventy-four hours after confinement.

This infant became jaundiced the third day following delivery. Upon examination the liver and spleen were just palpable below the costal margin. The blood study revealed: Hb. 81 per cent, red blood cells 3.8 million, and 10,550 white cells. Only 1 per cent normoblasts were present on smear. The jaundice disappeared on the seventh day but pallor became pronounced. The child became listless and nursed poorly. The hemoglobin had dropped sharply and reached 53 per cent. The red blood cells numbered only 2,260,000. Sixty cubic centimeters of citrated blood were accordingly administered. As there was no improvement, a second transfusion of 80 c.c. was administered on the ninth day. Recovery thereafter was rapid. The baby was discharged on the twelfth day after birth in good condition.

SUMMARY AND CONCLUSIONS

1. Erythroblastosis fetalis is a disease of the blood-forming organs of the newborn and neonatal infant, which results in an anemia characterized by the presence of an excessive number of immature red blood cells in the circulation.

2. Hydrops fetalis, icterus gravis neonatorum, and anemia hemolytica neonatorum are the three clinical types of erythroblastosis. Overlapping features are not infrequent. Five infants in the icteric group presented circumscribed edema. Icterus was the first symptom in the three infants of the anemia group.

3. Erythroblastosis fetalis is not rare. Twenty-seven cases were encountered in 15,334 deliveries, an incidence of 1 in every 568 confinements. There were 4 cases of hydrops fetalis, 1 in 3,833; 20 cases of icterus gravis, 1 in 766, and 3 instances of anemia hemolytica, 1 in 5,111.

4. Persisting hematopoiesis in the liver and spleen is the dominant pathologic finding. The bone marrow is hyperplastic. Extramedullary hematopoiesis is often encountered in the pancreas, kidneys, and suprarenal glands.

5. The blood picture is distinctive. The hemoglobin and red cells are reduced but the color index is above standard. The total number of nucleated cells is increased with an abnormally high ratio of early red blood cells (normoblasts and erythroblasts).

6. A tendency for recurrence in successive pregnancies is noteworthy. Four such cases are reported in 19 mothers of the icteric group.

7. Recurrent stillbirths were observed in 75 per cent of mothers with hydropic children, and in 21 per cent of mothers who had delivered icteric progeny.

8. Multiparas are generally affected. The average parity for the entire series was 2.8.

9. Toxemia of pregnancy is above the normal incidence but of only moderate severity. It was noted in 50 per cent of the hydrops group and in 20 per cent of the mothers in the icteric group.

10. Premature labor is frequent. It was encountered in all of the hydrops cases and in 30 per cent of the icteric series. In hydrops fetalis the distended abdomen may cause dystocia. This was observed in 2 of 4 infants in the series.

11. Hydrops fetalis is the fatal type of erythroblastosis. All 4 infants in this group perished. Subcutaneous edema, ascites, enlargement of liver and spleen are the important clinical findings. The large edematous placenta is noteworthy.

12. Intrapartum diagnosis of hydrops fetalis is possible by x-ray examination. It should be routinely employed where a history of recurrent stillbirths or definite erythroblastosis is obtained.

13. Icterus gravis is a severe form of erythroblastosis. Fifteen of 20 infants succumbed. Jaundice is the most prominent symptom, but may not appear for twenty-four to forty-eight hours after birth. Enlargement of the liver and spleen is present. The blood picture is

typical. The basal ganglia may show biliary pigmentation ("kernicterus"). Four such instances were found on post-mortem examination. Cerebral hemorrhage is frequent and often precludes recovery. The placenta is grossly normal.

14. Anemia hemolytica neonatorum is the mildest form of erythroblastosis. All 3 infants recovered. Pallor of the skin and mucous membranes may be anteceded by mild icterus. Enlargement of the liver and spleen, or both, and an increased number of normoblasts in the smear afford prompt diagnosis.

15. Early and repeated transfusions comprise the ideal method of therapy for icterus gravis. The 5 infants who recovered received such prompt treatment. Iron and liver extract are valuable adjuncts to transfusion in the anemia group.

16. A history of repeated stillbirths indicates careful search for erythroblastosis as the underlying cause. Where autopsy is not obtainable smears made from cord blood afford a prompt and efficient method of diagnosis.

We extend our thanks to Dr. M. Lederer for permission to review the autopsy material and to the members of the Departments of Obstetrics and Gynecology for the privilege of including their cases.

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The author presents a summary of all available information regarding the physiology and disturbances of vitamin metabolism in the gynecologic-obstetric field. The problems of avitaminosis are not of as great importance in this field as are the effects of hypovitaminosis. Not only does this condition depend upon intake but it is suggested that disturbances in the physiology of structures concerned in the final production of active vitamins (the liver and vitamin A, the skin and vitamin D) may play a part in the resultant hypovitaminosis. Known deficiencies in vitamin E in pregnancy and lactation are pointed out and the effects suggested. What little is known of the relationship of vitamin E to fertility is described.

An excellent case is made in stressing the lack of information available in this field and the probable value to be obtained from investigation. Very little is known of the results of hypovitaminosis as compared to avitaminosis, and it is in the former that the most pressing problems lie. No original or new work is presented.

J. L. McKelvey.

RELATIONSHIP OF THE THYROID AND ADRENAL GLANDS TO THE TOXEMIAS OF PREGNANCY*

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THE toxemias of pregnancy have presented a complex problem, in which there has existed an alteration in the chemistry and physiology of the body, producing the pathologic lesions which have been characteristic of the disease. Recent investigative work has brought forth the relationship of the electrolytes and hormones to these changes, and a decision as to their behavior may help to solve the mystery that surrounds the etiology of these conditions. The toxemias are problems far too intricate for the obstetrician alone to decide, and the expert opinion and judgment of the chemist, physiologist, histologist and pathologist are necessary to understand these unusual physical changes.

The purpose of this paper is not to promote any new theory concerning these things, but rather to review the work which has been done on them. The data which have been prepared have been obtained through the cooperation of the departments† of chemistry, physiology, histology, and pathology.

In order to more clearly understand the material presented, a short résumé of the recent research on the toxemias is presented, limiting the discussion to the glandular relationships.

Cushing was among the first to consider the possibility of glandular involvement in these conditions. He stated that a basophilic infiltration of the pars nervosa of the pituitary had occurred in eclampsia. Others found that associated with these infiltrations were similar changes in the cortex of the adrenal glands. Hofbauer stated that the toxemias were based upon a pituitary-adrenal relationship. George Van S. Smith, O. Watkins Smith, Rovak, Taylor and others have observed the importance of the anterior portion of the pituitary by the increase of prolan that occurs in the late toxemias. However, there is some question as to the source of this prolan. Taylor and associates have recently presented good evidence that there exists a relationship of estrogen and other placental hormones to the sodium and potassium balance during pregnancy. Thus, they have considered the ovary and placenta as factors in production of these conditions. Bartholomew and Colvin stated that adolescent gravidas with basal metabolic rates below plus 10 showed hypercholesteremia, and were increasingly subjected to toxemias as the basal metabolic rate decreased. In 1934, I reported a series of 1,250 basal metabolic rates during pregnancy, in which a relationship between the level of metabolism and the early as well as late toxemias seemed to exist. In these studies the thyroid seemed to have some relationship to the toxemias.

*Read at a meeting of the Brooklyn Gynecological Society, March 1, 1940.

†For their valuable aid I am gratefully indebted.

It might be assumed from the foregoing that there must exist an imbalance of the glands of internal secretion during these conditions. However, we are impressed by the tremendous variation that may produce symptoms and signs, if we examine the values of these in any of these groups. In some, high concentration of hormones seems to produce symptoms, while in others nothing abnormal develops. It would appear that development of toxemia depends upon the ability of the individual to withstand the great glandular and metabolic changes that take place during pregnancy. We have been interested in the adrenals and thyroid during pregnancy and the toxemias, and feel that they play an important part in the production of some of the abnormal physiology that takes place during these conditions.

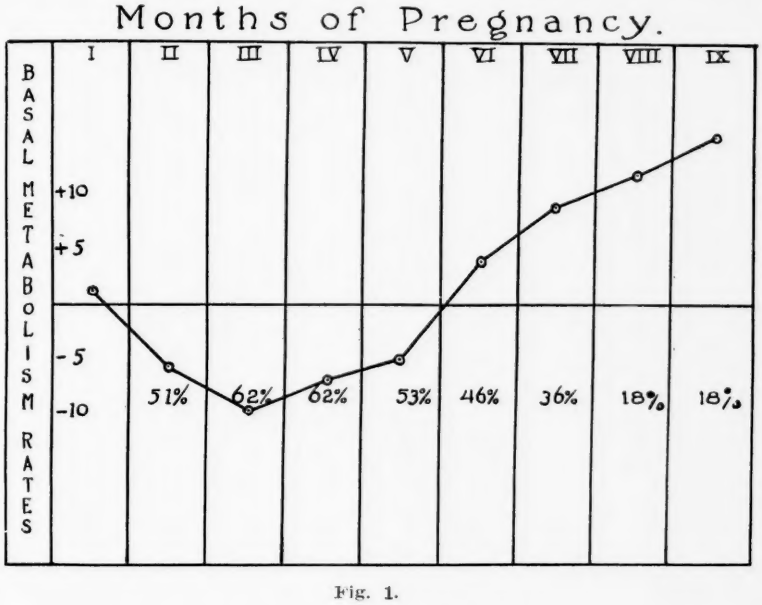

Fig. 1.

The following problems will be considered:

1. The relationship of the basal metabolic rate to the early and late toxic groups will be discussed.

2. The level of sodium in blood serum and urine in normal and abnormal pregnancy will be related.

3. The effect of injection of the urine of toxic patients upon the thyroid, adrenals, liver, and kidneys of rabbits will be described.

The relationship of the basal metabolic rate to normal pregnancy and the toxemias of pregnancy has been observed in a series of 400 private patients, therefore conditions could be made as basal as necessary. These findings differed slightly from those reported earlier, showing the advantage of a larger group of cases. These will be reported in detail elsewhere.

OBSERVATIONS

During the first trimester, there was a tendency for the basal metabolic rate to be below the zero line (Fig. 1). In the second and third months, the reading was below zero in 51 per cent and 62 per cent of the cases, respectively. During the second trimester, the readings showed an increase, and a greater percentage approached the zero line. In the fourth, fifth, and sixth months, the readings were below in 62 per cent, 53 per cent, and 46 per cent of the cases, respectively. During the third trimester, the rate had increased above the zero line, so that 63.3 per cent, 82 per cent, and 82 per cent were above zero in the seventh, eighth, and ninth months, respectively. In presenting this curve, it was realized that the values were within normal limits. However, the trend of the curve was the important observation, being below zero in the first trimester and above zero in the last trimester.

During the first trimester, many patients complained of the symptoms of subnormal metabolism, namely fatigue, exhaustion, and drowsiness. Certain other symptoms and signs also occurred during these months. Their relationship to the level of metabolism was noted in the four following groups of cases:

1. Those with basal metabolic rates above plus 10.
2. Those with rates between 0 and plus 10.
3. Those with rates between 0 and minus 10.
4. Those with rates below minus 10.

TABLE I

CASES 400	BELOW −10 %	0 −10 %	0 +10 %	ABOVE +10 %
Moderate nausea	62	68.0	26.2	18.0
Moderate vomiting	61	40.0	10.3	10.0
Severe nausea	36	7.6	0	5.0
Severe vomiting	36	7.6	0	2.6
Fatigue	66	66.0	15.0	14.0

The percentages of the occurrence of early symptoms and signs are shown in Table I. Many patients showed a considerable drop in the metabolic rate as the symptoms and signs occurred. It was also apparent that thyroid given to these women did not improve the symptoms appreciably nor cause the usual elevation in the metabolism rate.

During the second trimester, the basal metabolic rate approached the normal. During these months, the hormonal content of the body was more balanced and few complications occurred.

During the third trimester, there occurred an elevation in the basal metabolic rate, the majority of the cases rising above zero. This was probably due to the excess hormonal production, increased weight, surface area, and protoplasmic mass. However, in several cases of twins and one case of triplets, the basal metabolic rate did not increase more than usual. The relationship of the development of pre-eclampsia and eclampsia was observed during this time. Eclampsia did not develop. Pre-eclampsia developed more often in the following types of patient:

1. When the basal metabolic rate was abnormally low during the first trimester, and failed to increase during pregnancy.

2. When the basal metabolic rate dropped appreciably to a low value and remained at this level throughout pregnancy.

In these groups, pre-eclampsia occurred five times more often than in the other groups. However, as the toxemias developed, the metabolism increased quite rapidly.

As a test of the value of basal metabolic rates during pregnancy, two series of patients were studied. The first series comprised 550 patients. In these cases, the prenatal care was thorough and adequate, but the metabolism was allowed to take its own course. Pre-eclampsia occurred in 5.2 per cent of the cases.

In the second series of 558 private patients, the same amount of prenatal care was given, but all patients with metabolism below zero were given thyroid extract in adequate doses to maintain a constant plus level. The incidence of pre-eclampsia in this group was 2.5 per cent. From these results it is felt that it is important to follow the basal metabolism from the onset of pregnancy.

The second portion of this paper deals with the effect of normal pregnancy and the toxic conditions of pregnancy upon the metabolism of sodium. Sodium is perhaps the most important base in the body, and is absolutely necessary for life. It is carried by the serum and the intercellular fluids almost entirely, and remains at a constant level. Among the conditions which alter the level of sodium in these fluids, perhaps insufficiency and overactivity of the adrenal cortex have the greatest influence. If the former condition prevails, sodium is lost

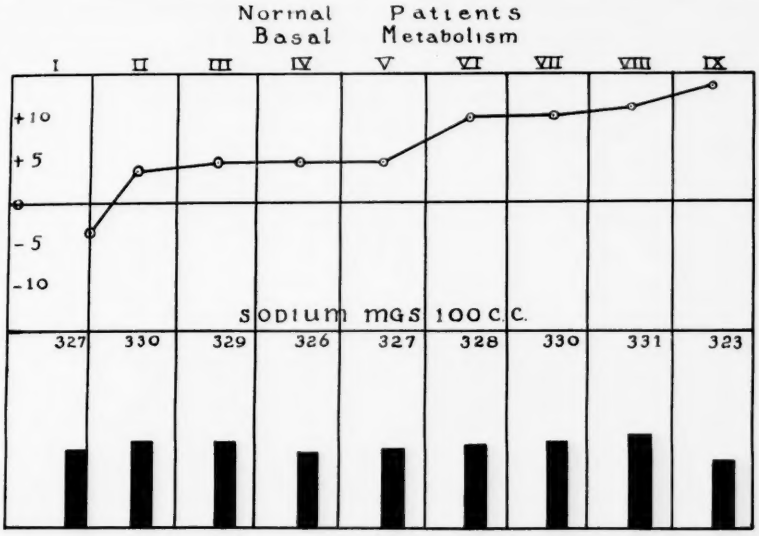

Fig. 2.

readily through the urine, thus causing a depletion of the sodium in the blood serum. If the latter condition develops, sodium is retained with water in the tissues. Other conditions causing loss of sodium are excessive vomiting, sweating, and diarrhea. During normal conditions, the intake and output of sodium maintain a constant balance, most of the sodium being excreted through the kidneys. Recent work has indicated that the metabolism of sodium is controlled by the adrenal cortex, and that reduction in the function of that gland is indicated by a high urinary output and a low serum value. Whether this criterion would be true during pregnancy when so many other factors are involved, is not known.

Sodium was determined in the serum and urine by using a modification of the Butler-Tuthil method. Values were expressed in milligrams per 100 c.c. of serum. Sodium determinations were made in three groups of patients:

1. Normal patients during pregnancy.
2. Patients suffering from mild and severe, early toxic conditions.
3. Patients having pre-eclampsia and eclampsia.

The first group consisted of 52 normal pregnant women. These individuals were placed upon diets containing 5 gm. of sodium and 10 glasses of water per day. It was impossible to place these women upon an absolutely controlled diet. However, careful instructions were given as to the diet, and it seemed accurate enough to be comparable. The values were surprisingly uniform. Basal metabolic tests were also done on the same day that the sodium was determined. In these patients no symptoms or signs occurred. Results are recorded in the following chart (Fig. 2).

The second group were patients suffering from nausea and vomiting of early pregnancy, and were classified as follows:

A. Twenty patients with nausea alone.

B. Twelve patients having emesis gravidarum.

Both groups were placed upon an intake of 5 gm. of sodium per day. The output of sodium was not recorded. These patients were not considered controlled studies, and were treated in the home or office.

C. Seven patients were classified as hyperemesis gravidarum.

These patients were all treated in the hospital and were seriously ill. Therpeutic abortion was necessary in two cases. Death occurred in one ward case. This group was carefully controlled for three days. Five grams of sodium were given in 2,100 c.c. of 5 per cent glucose intravenously per day. Nothing was given by mouth during the control period, so the amount of vomitus at each eructation was very small. Sodium estimations were made upon the vomitus and urine, but were not calculated upon the stool. It is interesting to note that the output of sodium in the urine was nearly equal to the intake (Tables II and III).

TABLE II. BASAL METABOLIC RATE AND SODIUM DETERMINED IN EARLY TOXEMIAS

	GROUP I (NAUSEA)	GROUP II (EMESIS GRAVIDARUM)	GROUP III (HYPEREMESIS GRAVIDARUM)
Total cases	20	12	7
Average blood pressure	115-80	94-80	90-60
Acetone in urine	0	36%	100%
Loss of weight	30%	93%	100%
Fatigue	50%	100%	100%
Sodium-Serum			
During symptoms	313.6 mg.	306.2 mg.	288.3 mg.
Lowest sodium	311.0 mg.	298.0 mg.	262.5 mg.
Highest sodium	323.0 mg.	314.0 mg.	305.0 mg.
After symptoms	325.3 mg.	326.8 mg.	325.4 mg.
Basal metabolic rate			
Drop from normal	60%	90%	*100%
Per cent below 0	85%	84%	-100
Average	-9	-11	- 18

*Only 3 patients had basal metabolic rate on account of condition.

TABLE III. CONTROLLED GROUP

	HYPEREMESIS GRAVIDARUM	
Total cases	7	
Intake	2100 c.c. daily	
Output	1950 c.c. daily	
Sodium		
Average intake	5000.0 mg.	5.0 Gm.
Average output—urine	4029.5 mg.	4.02 Gm.
Average output—vomitus	700.0 mg.	0.700 Gm.
Average sodium-serum	288.0 mg.	0.28 Gm.
Average low	262.5 mg.	0.26 Gm.
Average high	305.0 mg.	0.30 Gm.

Two patients presented some notable findings. In one, the blood plasma sodium reached a level of 262 mg. per 100 c.c. of serum. At this point, the patient was in severe shock, blood pressure and pulse imperceptible, and condition was very grave. The excretion of sodium in the individual was very low, the average being 26.6 mg. per day. However, the output of urine was very scanty, total 450 c.c. per day. This showed that when the sodium and chloride reached a dangerously low level, the kidneys either attempted to restrict their output, or were so severely damaged that they failed to excrete.

The second patient, after the control period, was given 10 Gm. of sodium with 5,000 c.c. of fluid per day. The output of urine about equalled the intake, and the sodium excretion rose to 12.5 Gm. This shows that the output of sodium is also dependent upon the output of water. With a low threshold of sodium in the kidneys that may exist at this time, the water washes the sodium out of the system sooner than it would during the normal states.

It was also noted that of the 5 patients cured of hyperemesis, 2 became toxic in the latter months of pregnancy and labor had to be induced. In these women, the level of sodium was slow to rise to normal, and not until the normal was reached were these women free from symptoms.

Sodium determinations were made in three groups of patients presenting the typical picture of the true late toxemias of pregnancy. The type of onset and follow-up examinations substantiated these facts. There occurred the usual

TABLE IV. LATE TOXEMIA GROUP—UNCONTROLLED

	PRE-ECLAMPSIA	ECLAMPSIA
Total cases	12	6
Av. Blood pressure	182-115	186-126
Edema	100 %	100 %
Albumin	1+—0.30%	0.10%—0.44%
NPN	27	24
Total proteins	5.7	5.6
Fluid		
Av. intake	1776 c.c.	2100 c.c.
Av. output	810 c.c.	700 c.c.
Sodium	Serum—mg. per 100 c.c.	
During condition	304.4	298
After delivery—10 days	327.2	329

TABLE V. CONTROLLED GROUP

	PRE-ECLAMPSIA	
Total cases	14	
Fluids—average		
Intake	2100 c.c. daily	
Output	1188 c.c. daily	
Sodium	Serum—mg. per 100 c.c.	
Av. during control	307.3 mg.	
Lowest Na	295.0 mg.	
Highest Na	317.0 mg.	
Sodium		
Average intake	5000.0 mg.	5.0 Gm.
Average output, per 24 hr.	1728.4 mg.	1.7 Gm.
Av. output, per 100 c.c. urine	162.5 mg.	0.162 Gm.
Lowest output, per 24 hr.	575.0 mg.	0.57 Gm.
Highest output, per 24 hr.	2873.0 mg.	2.8 Gm.
Lowest output, per 100 c.c.	57.0 mg.	0.057 Gm.
Highest output, per 100 c.c.	268.0 mg.	0.268 Gm.

disturbance in water balance, as shown by the presence of edema, low plasma proteins, scanty urine, and albuminuria. The usual symptoms and signs, such as headache, disturbance of vision, and high blood pressure, were also present. Although the patients in Groups I and II were placed upon 5 Gm. of sodium intake, they were not controlled studies.

The third group consisted of 13 cases of pre-eclampsia. In this group, a simple diet of milk, orange juice, toast, crackers, and sodium to make a total of 5 Gm. per day, was given. The total fluid intake was 2,100 c.c. per day. There was no vomiting. Sodium excretion by bowel was not determined. The urinary output was carefully estimated. The data are as shown in Tables IV and V.

DISCUSSION

In consideration of these findings, it would seem that the level of sodium was disturbed but little during normal pregnancy. In abnormal conditions, such as nausea and vomiting that occur in the first trimester of pregnancy, the threshold for sodium in the kidneys may be at a lower level than normal, and allow this base to be excreted more readily. Also, sodium was probably lost in the vomitus to a greater extent than even shown in these studies, because in these particular patients the amount of vomitus was small as compared with the average case. The loss of sodium in these two ways reduced the amount in the serum to unusual and dangerous levels.

The balance of sodium was again disturbed when pregnancy was complicated in the last trimester by preeclampsia and eclampsia. In these cases, where the intake of sodium was the same as in the other group (namely 5 Gm.), the amount of sodium in the blood serum was again low (average 297 to 304.4 mg.). The excretion of sodium by the kidneys was considerably less than normal or in the early complications. The first question that arose was how to explain the low serum value when the output of sodium through the kidneys was so small. Our tentative interpretation was as follows: The serum proteins were below normal, probably being lost in the urine. This caused the osmotic pressure in the capillaries to be diminished. This fact, coupled with the rise in blood pressure and increased permeability of the capillary wall, drove the fluid into the tissue spaces. The sodium was moved with the water and passed into the tissues. There occurred an actual retention of sodium and chloride, even though the concentration in the serum was below normal. In other words, the amount of sodium is the same per 100 c.c. of serum as it would be per 100 c.c. of tissue fluid. As soon as the kidneys started to put out water after delivery, then sodium was abstracted from the tissues into the circulation and was excreted. Just that situation occurred after delivery of these patients. The urinary output increased markedly, and again the sodium in the serum was at a low level, owing to the rapid excretion in the urine.

The next question that presented itself, was what influence upon the kidneys was present during these times which would cause sodium to be excreted more readily during the early toxic conditions and retained during the late conditions. Also, what had caused the proteins to be lost in the urine so readily in pre-eclampsia and eclampsia. Taylor and associates had considered that the estrogenic and placental hormones had influenced the sodium and potassium excretion. Engel

and Thorn had thought that the edema during the menstrual period was caused by progesterone. Inasmuch as the adrenal cortex controls the sodium and perhaps the water metabolism, this structure could also play an important part in the production of edema. If any of these products of glandular activity had produced these changes, their presence should be found in the urine in abundance. With this thought in mind, urine from those patients described earlier was injected into rabbits in an attempt to reproduce the pathologic findings of these toxic conditions. All rabbits were mature virgins, weighing approximately 3000 Gm.

Sixty cubic centimeters of urine were given intravenously in each case, and the animal killed by a blow on the neck fifty-two hours later. They were autopsied immediately. Although all of the endocrine glands are being studied, only the effect on the thyroid and adrenals will be reported at this time. The effect on the liver and kidneys will also be reported.

Five groups of rabbits were studied:

1. Six rabbits were injected with 60 c.c. of urine from normal patients eight to ten weeks pregnant.

2. Four rabbits were injected with 60 c.c. of urine from patients described earlier in this paper as hyperemesis gravidarum.

3. Ten rabbits were injected with 60 c.c. of urine from patients classified as pre-eclampsia and eclampsia.

4. Seven rabbits were injected with 60 c.c. of urine from normal pregnant women at term.

5. Ten pregnant rabbits were killed at various stages of their pregnancy. They had not been injected.

On account of the lack of space, it is impossible to show the structures of Groups 4 and 5. Examination of these structures showed normal thyroid and adrenals with the exception of some hyperplasia as term approached. Also, there were no liver or kidney changes. There was some slight change in the thyroid, adrenals, liver, and kidneys of those rabbits injected with term urine. However, these changes were not considered significant.

The changes in the structures of Groups 1, 2, and 3 will be shown in Figs. 3 to 11.

Injection of urine from normal, early pregnant patients, and those suffering from hyperemesis gravidarum has produced changes in the structures of the thyroid and adrenal glands of the rabbits. Examination showed the follicles of the thyroid were uniformly large with a store of colloid. The cells lining these follicles seem uniformly flat with small nuclei. These findings would indicate a gland of low activity. The adrenals of these same rabbits also showed signs of altered function. The cells of the reticular layer of the cortex showed some unusual characterization. Some cells were gathered in clusters, and the cytoplasm was very pale, vacuolated and without granulation. The nuclei were also shriveled, pushed to one side and were smaller than normal. Some whole cords of cells were affected in a similar manner, the extension reaching to the glomerular zone. These cells did not take a fat stain. Inasmuch as these rabbits were all mature and of good size, any change that would take place in early life could be ruled out. There occurred necrosis with hemorrhage about the central vein in the liver of three of the four rabbits in Group 2. Also, there

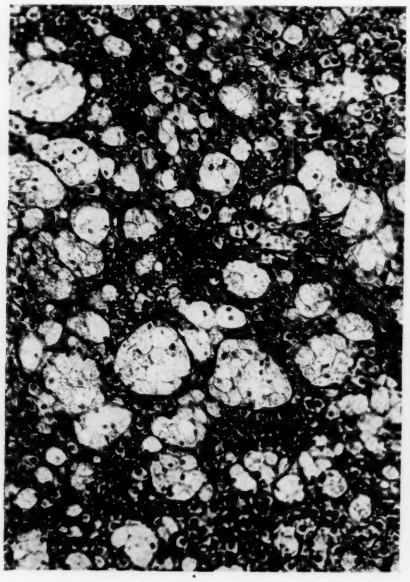

Fig. 3.

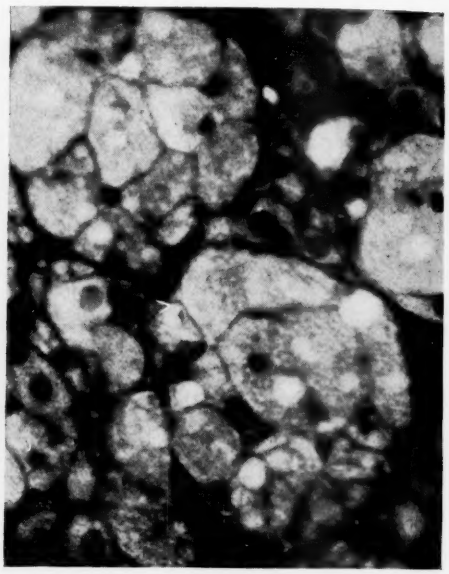

Fig. 4.

Fig. 3.—Adrenal cortex. Low power ×150. Rabbit I, injected with 60 c.c. of urine from a patient ten weeks pregnant. Patient had nausea and vomiting of moderate degree. Vacuolated cells shown in Figs. 1 and 2 were found in the reticular zone of the adrenal cortex.

Fig. 4.—Adrenal cortex. High power ×600. Rabbit I. Cluster of cells showing vacuolation. Nuclei of these cells are shriveled and pushed to one side. Cells distended, possibly early degenerative changes.

Fig. 5.

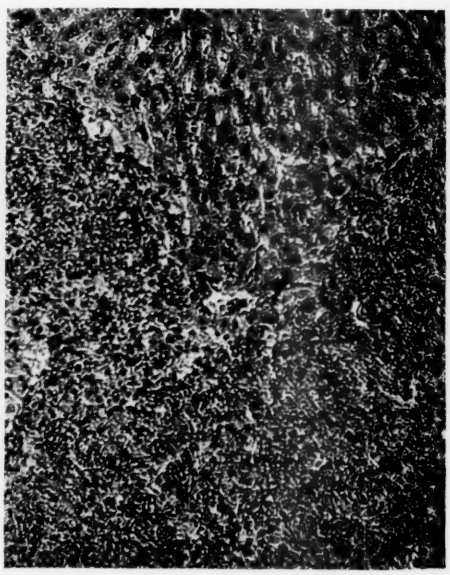

Fig. 6.

Fig. 5.—Thyroid. High power ×600. Rabbit I. Follicles are uniformly large, filled with colloid. Cells lining the follicles are flat with elongated nuclei. Low activity gland.

Fig. 6.—Liver. Low power ×150. Rabbit H. Necrosis with hemorrhage occurred about central vein. Fatty degeneration occurred about central vein, also.

occurred a bleaching out of the cells about the central vein in three rabbits, and distinct necrosis with hemorrhage in two others of Group 1.

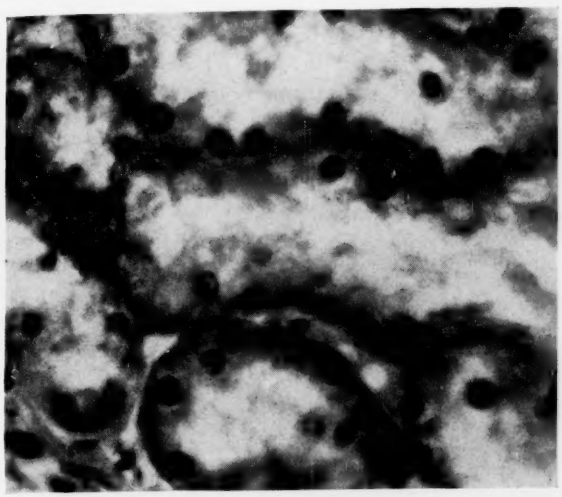

Fig. 7.—Kidney. High power ×600. Rabbit I. Sloughing of cells of the proximal secreting tubules.

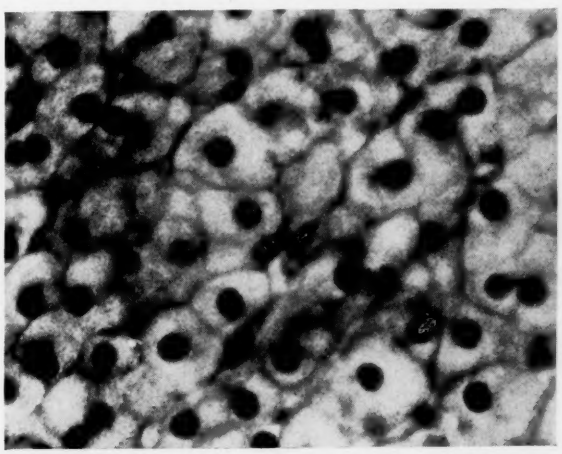

Fig. 8.—Adrenal cortex. High power ×600. Rabbit M. This rabbit was injected with 60 c.c. of urine from an eclamptic patient seven months pregnant. Cells are smaller, no vacuolization, cords of cells were longer, and cells appear more active.

The damage in the kidneys was not as extensive, but there was some sloughing of the cells in portions of the distal and proximal secreting tubules. These changes were even more marked when injected into pregnant rabbits.

The structures from rabbits in Group 3 have shown a different picture. The thyroid seemed to be one of activity. The average follicle was smaller with less colloid. In some follicles the colloid had nearly disap-

peared. They were lined by more cuboidal types of cells. The nucleus was larger and more active. The adrenal cortex also appeared different. The cells were smaller, the cords were longer and appeared more active. The large, vacuolated cells observed in Groups 1 and 2 did not occur in a single case. There were more mitotic figures in the glomerular area.

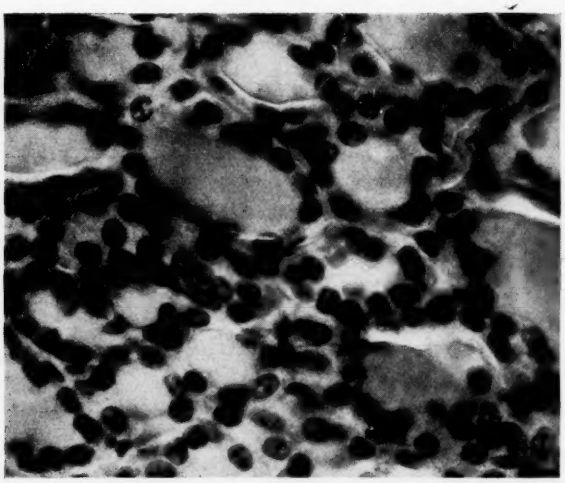

Fig. 9.—Thyroid. High power ×600. Rabbit M. Follicles are uniformly smaller and contain less colloid. The cells lining the follicles are more colloidal with more oval nuclei. The gland appears to be more active.

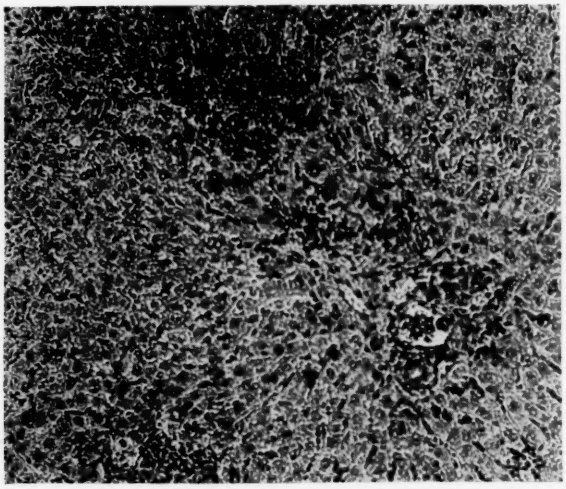

Fig. 10.—Liver. Low power ×150. Rabbit M. Area of necrosis with hemorrhage occurred about the outside of the lobule or periportal. Fatty degeneration also occurred about the same area.

The liver from these rabbits also presented a different picture. In 5 rabbits, the cells about the periphery of the lobule were involved. Necrosis and hemorrhage appeared here. The kidney likewise showed the sloughing of cells in the distal portion of the secreting tubules.

It would appear that some product of metabolism or some other material, perhaps hormonal in nature, had been produced in these patients where a general metabolic change had occurred, and also where the sodium content was altered. This material had been excreted in the urine, which when injected into rabbits, produced the changes in the structures described previously. These lesions were typical of those found in early and late toxemias.

When considering what the nature of this material might be, many possibilities arise. The question of the influence of the hormones of the anterior lobe of the pituitary and those l. mones simulating those from this gland is important. It would seem that if these conditions were due to these structures the findings would be the same when urine from early and from late toxic cases were used. However, this

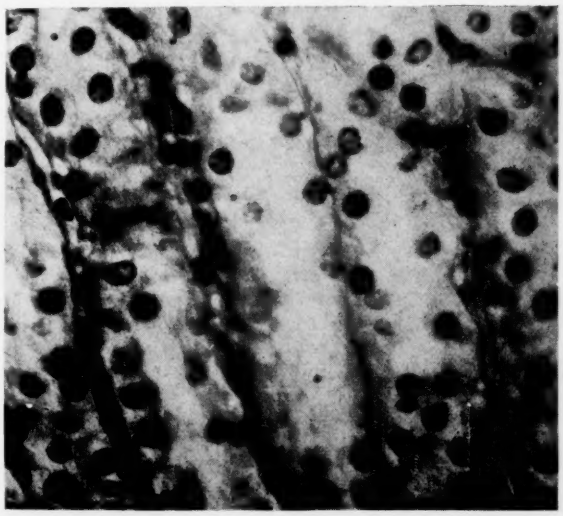

Fig. 11.—Kidney. High power ×600. Rabbit M. Sloughing of the cells lining the distal secreting tubules is shown.

did not occur, the thyroid and adrenals differed in each group, and the lesions in the liver occurred at opposite sides of the lobules. Therefore, it would seem either that the high prolan values found to occur in the later toxic conditions were from a different source or of a different type, possibly placental in origin. Also the question arises if the cortex of the adrenal glands might not be the offending structure, being depressed in function early in pregnancy and overactive in late pregnancy. Also, the placenta and fetus cannot be forgotten as producing hormones yet undiscovered, which may explain all of these conditions. Then the possibility of the corpus luteum becoming too active brings up another source of material. If we disregard the hormone situation, the discussion takes us to some metabolite, perhaps an animo acid. In any event, further work must be done, and perhaps by the combined efforts of all, some advances will be made to solve the mystery which surrounds these conditions.

CONCLUSIONS

1. Basal metabolic rates indicated that pregnancy has an affect on the glands controlling metabolism. This was indicated in the first and third trimesters.

2. Administration of thyroid to those with low rates in the first trimester reduces the incidence of the late toxemias 50 per cent, but must be given early in pregnancy.

3. Serum sodium is lowered during the early and late toxemias, but remains constant throughout normal pregnancy.

4. Sodium is excreted in the urine in greater quantities in the early than in the late toxemias.

5. Sodium in the serum is lowered in pre-eclampsia and eclampsia because of loss of serum protein and water accumulation in the tissue spaces.

6. Injection of early and late toxic urine into virgin rabbits produces lesions in the thyroid and adrenals. The pathologic changes in the liver and kidneys were typical of early and late toxemias of pregnancy.

7. The late group of toxemias presented a different hormonal picture from the early.

8. The question arises as to whether these changes mean hormonal imbalance, or overproduction of some toxic metabolite, or both.

I wish to express my sincere gratitude to the Departments of Chemistry, Microscopic Anatomy, Pathology and Physiology for their cooperation in this work.
I also wish to express my appreciation to Miss Anne Coplon, technician, for her efforts.

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THE TREATMENT OF OLIGURIA AND ANURIA*

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THE definitions of oliguria (a diminished output of urine) and anuria (a suppression of urine) are inadequate in that no period of time is designated to constitute a diagnosis of either condition, and the amount of urinary output, as a criterion for the use of the term, is not specified. It is our opinion that oliguria should be defined as the excretion of less than 600 c.c. of urine within twenty-four hours, and anuria as the absence of urine for twelve or more hours. Thus the occurrence of oliguria would be quite frequent in obstetrics, but anuria would be rare.

Oliguria or anuria is found with varying degrees of frequency in the following conditions:

Toxemia of pregnancy (eclampsia, pre-eclampsia).
Dehydration:
(a) Due to loss of water (hyperemesis gravidarum, prolonged abdominal operations, peritonitis, intestinal obstruction, and diabetic coma).
(b) Due to loss of blood (abruptio placentae, post-partum hemorrhage, placenta previa, rupture of the uterus, and ectopic pregnancy).
Blood transfusion reactions (incompatible and compatible blood).
Shock.
Ligation of both ureters.
Cortical necrosis of the kidneys.

We have previously described the treatment of a number of these conditions, and, therefore, we shall limit our remarks to the treatment of oliguria associated with blood transfusion reactions.

It is most difficult to treat oliguria and uremia following an incompatible blood transfusion. The mortality rate due to blood transfusion, according to various reports, ranges from 0.013 to 1.3 per cent; almost all the deaths are preventable. We have given over 1,200 blood transfusions since 1931, with evidences of serious reactions in 8 cases. We know that 4 patients were given incompatible blood, 3 received less than 100 c.c., and 1 received over 500 c.c., but none died. All patients had hemoglobinuria, but only the latter patient had uremia. Four other patients were given what was thought to be compatible blood and all died. Chemical analyses done on two patients revealed that the blood nonprotein nitrogen was 241 and 213 mg. per cent, respectively. Oliguria was present in all patients and serious infection was also an important factor in 3, but if the renal function had been normal it is presumed that all of them would have recovered.

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Over 300 blood transfusions were given on the obstetric service of Washington University, with one case of uremia, with recovery. The patient was given compatible blood, but developed oliguria, with a blood nonprotein nitrogen of 138 mg. per cent. Eight hundred cubic centimeters of a 30 per cent glucose solution were injected intravenously, twice daily, for seven days. Another patient, with an extensive carcinoma of the cervix, developed a puerperal infection following delivery, and was finally treated with radium. Donors, whose blood early in the puerperium caused no reaction, invariably caused hemoglobinuria after the radium treatment. This occurrence has not been noted in other patients after radium treatment, and we believe that the infection was a factor in producing heterologous hemagglutinins. We also had an opportunity to study a patient on another service who was given 500 c.c. of incompatible blood. The hemolysis of the erythrocytes produced a severe acidosis. The patient lived one and one-half hours. The CO_2 was 9 volumes per cent and the pH was 6.9.

Comparatively little importance is given in most hospitals to eliminating the dangers of blood transfusion. The typing, matching, and transfusion are usually performed by technicians and interns who have been given no instructions or have only a rudimentary knowledge.

DeGowin and co-workers have studied the cause and prevention of blood transfusion reactions, and they advise that one individual with experience should be in charge. All typing sera should be of high titer. They have five donors who were thought to belong to Group O and who gave transfusions, but were subsequently found to belong to Group A. One patient died from a transfusion given by one of these donors. It is important to check the donor's cells against the recipient's serum for both *agglutination* and *hemolysis*.

In attempting to determine the cause of the oliguria in one of our patients, we found that the cells were agglutinated, but hemolysis occurred so rapidly that the clumping was present for only a few seconds. One of the authors (W. J. D.) emphasizes the importance of matching the blood in small test tubes so that hemolysis can be seen. DeGowin states that hemolysis may occur without hemoglobinuria. Drabkin, Widerman, and Landow found that only 10 per cent of the hemoglobin disappearing from the plasma appears in the urine. DeGowin states that one should look for evidence of hemolysis in the blood serum within two hours after the transfusion.

Oliguria has been attributed to the following:

1. *Blocking of the Tubules by Precipitated Hemoglobin.*—Baker and Dodds have proved that this phenomenon occurs in rabbits, and DeGowin and co-workers found the same in dogs. Alkalinization of the urine will prevent oliguria in both dogs and rabbits after an intravenous injection of hemoglobin. The precipitated hemoglobin has been found also in the human kidney, but DeGowin has reported several cases of fatal oliguria and uremia after blood transfusion in which no hemoglobin was found in the tubules.

2. Renal lesions are due to a loss of chloride. Chemical analysis disproves this.

3. Anaphylaxis.

4. Nephrotoxic substances are set free by the hemolysis of the erythrocytes.

5. The liberated hemoglobin exerts a vasoconstrictor action on the renal vessels and the ischemia is the cause of the oliguria and renal pathology.

DeGowin concludes that there is still an additional unknown factor which causes the uremia. He advises that, whenever possible, the recipient's urine should be alkalinized prior to the transfusion.

A compilation of the cases of serious blood transfusion reactions reported by Goldring and Graef, Bordley, DeGowin, together with ours, reveals that there were 11 males, with 6 deaths, and 29 females, with 15 deaths. Thirteen of the females were obstetric patients, with 6 deaths, and 7 were gynecologic patients, with one death. We have referred in

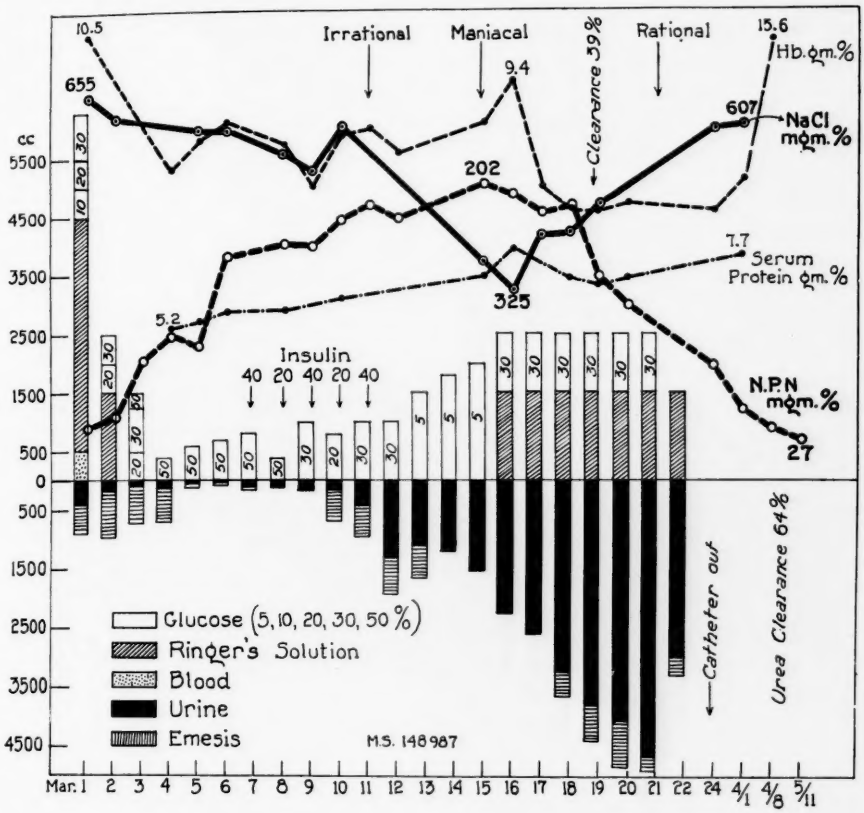

Fig. 1.—Chart showing oliguria and uremia due to an incompatible blood transfusion given in 1937. Examination of the patient on Feb. 6, 1940, revealed: Blood pressure, 100/80; urea clearance, 70 per cent; U/B, 7; serum protein, 6.9 Gm. per cent; and hemoglobin, 13.1 Gm. per cent. Urinalysis: Albumin negative; volume large; microscopic examination, essentially negative.

a previous article to the difficulty encountered in obtaining compatible donors for anemic patients with puerperal infection because of the marked rouleaux-formation of all erythrocytes suspended in the patient's serum. Therefore, for many years we have preferred to use Moss Group IV donors because their cells contain no agglutinogens. We also propose to adopt DeGowin's suggestion to alkalinize the urine of all patients who are given a transfusion.

The volume and the color of the urine should be examined carefully for forty-eight hours after every transfusion. If an oliguria or hemo-

globinuria is found, a hypertonic glucose solution should be injected intravenously in large amounts, and sufficient alkali also should be given intravenously to maintain an alkaline urine until the latter no longer contains hemoglobin.

The following solution will alkalinize the urine if the plasma CO_2 is within normal limits:

5 c.c. molar sodium lactate
25 c.c. distilled water
20 c.c. Ringer's solution
} Per kilogram of body weight

One-half of the solution should be given intravenously and the remainder by hypodermoclysis. One cubic centimeter of molar sodium lactate per kilogram of body weight given by mouth will maintain an alkaline urine, once the latter has been established. Twenty grams of sodium bicarbonate in a 5 per cent solution, given intravenously, may be used instead of the lactate, and this will raise the plasma CO_2 content approximately 15 volumes per cent in a woman weighing 60 kilograms, and also alkalinize the urine. The secretion of urine is stimulated by intravenous injections of 1,000 c.c. of a 20 per cent glucose solution given at intervals, in order to maintain a urinary output of at least 60 c.c. per hour. The amount of fluid given within twenty-four hours should not exceed the urinary output by more than 50 per cent. If the urinary output amounts to less than 600 c.c. within twenty-four hours, a 50 per cent solution of glucose should be given in 200 c.c. amounts every six to eight hours. No water should be given orally or rectally, as it not only does no good but may increase the vomiting, thus eliminating the chloride from the stomach, or it will cause edema if it is retained. Electrolyte solutions are of use initially and they should be used only after the first forty-eight hours, if an analysis of the blood reveals that they are requisite.

Data, in Table I and Fig. 1, illustrate the treatment of a patient who was given incompatible blood. This patient had a dilatation and curettage, with a blood transfusion, for an incomplete abortion. A marked hemoglobinuria developed and persisted for several days. It is evident that an anuria almost occurred. Two hundred

TABLE I. TREATMENT OF PATIENT GIVEN INCOMPATIBLE BLOOD

DATE	URINE			BLOOD	
	24-HR. VOL. (C.C.)	NaCl (GM. PER DAY)	N.P.N. (GM. PER DAY)	URIC ACID (MG. PER CENT)	CREATININE (MG. PER CENT)
3/ 1/37	400			4.5	4.6
3/ 2/37	180				
3/ 3/37	90	0.55	0.21		
3/ 4/37	140	0.18	0.09	10.9	11.1
3/ 5/37	60	0.13	0.06	10.9	15.0
3/ 6/37	30	0.15	0.06	13.8	17.5
3/ 7/37	105	0.52	0.17		
3/ 8/37	110	0.39	0.08	18.3	20.7
3/ 9/37	150	0.79	0.49	21.1	21.4
3/10/37	285	1.4	0.47	19.0	22.6
3/11/37	435	2.39	2.85	19.0	24.0
3/12/37	1300			18.9	22.1
3/13/37	1110	3.17	4.4		
3/14/37	1170	2.2	8.9		
3/15/37	1525	0.78	5.5	16.4	18.8
3/16/37	2250	2.38	13.3		
3/17/37	2600	2.38	15.2	11.2	16.7
3/18/37	3250	2.98	14.6	9.7	15.4
3/19/37	3800	3.42	12.6	9.2	12.1
3/20/37	4050	2.85	6.3	5.6	10.6
3/21/37	4700	7.17	11.7		
3/22/37	3000	10.0	8.9		
3/23/37	3260	8.54	6.9		
3/24/37	3450	7.28	6.1		
3/25/37	4660	11.9	9.97		

cubic centimeters of a 50 per cent glucose solution were given three or four times daily. Insulin was added to the solution to aid in metabolizing some of the glucose. The decrease in plasma chloride was attributed to the loss in the vomitus, the daily excretion in the urine of 2 to 3 gm., and the redistribution in the body due to the glucose injection. The serum protein concentration slowly increased to normal, indicating that sufficient glucose had metabolized to permit protein formation instead of destruction.

We have made extensive studies of two other patients with oliguria and uremia after blood transfusions, and three with uremia due to renal pathology (one proved and one presumable cortical necrosis, and one nephrosclerosis). The blood and urinalyses were essentially the same in all cases. The first urinalysis, in all instances, showed very little solids, and the chloride and nonprotein nitrogen concentrations remained very low for a number of days. The increase in the amount of these substances was first due to the increased volume of urine. The concentration also increased eventually. The blood uric acid and creatinine began to decrease as soon as the urinary volume was 1,000 c.c. or more, but the blood nonprotein nitrogen did not begin to fall until the urinary excretion was 13 gm. or more.

When an oliguria or an anuria develops, the usual tendency is to give large amounts of water by mouth and by rectum. Water and electrolyte solutions are excellent diuretics, but they are usually contraindicated in patients with oliguria or anuria due to toxemia, blood transfusion reactions, etc., unless a chemical analysis reveals a deficiency. Physiologic salt and Ringer's solutions are of value in patients with a diminished urinary output due to dehydration and hemorrhage. Of course, blood is necessary when the true hemoglobin concentration is below normal.

In the treatment of oliguria and anuria, glucose, the normal sugar found in the blood, can be injected in large amounts without danger. The prolonged administration of hypertonic glucose solution in dogs will produce a hyperpyrexia, due to dehydration, but this requires several grams of glucose per kilogram of body weight over many hours. When glucose is injected intravenously in amounts beyond the ability of the body to store, burn, and excrete in the urine, the blood sugar becomes elevated to as much as 1,000 mg. per cent. During the period of hyperglycemia there is a compensatory decrease in the concentration of electrolytes and also a blood dilution. The composition of the blood is remarkably constant and is governed by its osmotic pressure. If the concentration of one substance is increased, an equivalent osmolar decrease occurs in another.

This mechanism is illustrated by the data in Table II. Five hundred cubic centimeters of a 20 per cent glucose solution were given intravenously to one of the authors (W. J. D.) over a period of thirty-one minutes. There was a decrease of 13 per cent in the cell volume and a decrease of 26 per cent in the serum protein concentration during the injection, indicating an increase in the plasma volume, and the return within one hour to their initial concentration. The interferometer measures exactly the concentration of all the solutes in the plasma and the figures reveal a decrease of 17 per cent during the injection and a rapid return to the original reading. The direction of change, that is, dilution or concentration, of the hemoglobin, cell volume and serum protein, has always been the same, but the actual percentage of alterations usually differs. Glucose is not an electrolyte and exerts, roughly, one-fifth of the osmotic pressure of sodium chloride, which accounts for the apparent discrepancy between the concentration of glucose and sodium chloride. However, if

TABLE II. CHANGES DUE TO THE ADMINISTRATION OF LARGE AMOUNTS OF HYPERTONIC GLUCOSE SOLUTION

Time in minutes	0	16	31	100
Plasma NaCl, mg. per cent	586	573	555	590
Plasma glucose, mg. per cent	97	450	550	159
Cell volume, per cent	48.5	44.0	42.0	48.0
Interferometer reading	1145	1009	949	1152
Serum protein, gm. per cent (interferometer)	7.4	6.1	5.5	7.3
Serum protein, Kjeldahl	7.4	6.1	5.4	7.4
Plasma CO_2, volume per cent	58	68	62	65
Nonprotein nitrogen	20	21	24	22
Osmolar Equivalents—Calculated in mM.				
Plasma NaCl	200	195.8	189.8	201.4
Plasma glucose	5.8	26.7	32.6	9.4
Plasma CO_2	52.9	61.9	56.4	59.2
Serum protein	15.3	12.7	11.5	15.1
Nonprotein nitrogen	2.5	2.6	3.0	2.7
Inorganic P (estimated)	5.6	5.6	5.6	5.6
Lactic acid (estimated)	4.2	4.2	4.2	4.2
Total	286.3	309.5	303.1	297.8
Osmolar Equivalents—Obtained				
Freezing point lowering	0.544	0.560	1.532	0.546
Osmolar equivalents, mM.	294.0	302.7	287.6	294.6

one calculates the osmolar concentration of each substance, the increase of glucose is compensated for by a proportionate decrease in the electrolytes. Determinations of the freezing point illustrate how close the balance of the osmotic pressure is maintained. During the injection, a marked diuresis occurred and considerable amounts of chloride were excreted in the urine, as well as small amounts of glucose. We have made similar observations, with added conductivity measurements in three other patients.

Sunderman and Williams have confirmed our work. In their study they administered 75 gm. of glucose orally to diabetic patients, and found that the increase in the concentration of glucose in the serum, as moles per kilogram of water, was accompanied by a decrease in the concentration of chloride in the same units in approximately the ratio of 3.8 to 1. Our ratio is 2.7 to 1.

Sucrose and another carbohydrate, sorbitol, each of which, in a 50 per cent concentration and in amounts of 100 to 200 c.c., have been used individually as diuretics. The renal threshold for glucose is approximately 180 mg. per cent. The threshold for the above substances is zero. They require, theoretically, only one-half the osmotic adjustments in the plasma as does glucose, and if the kidney is functioning sufficiently to excrete these foreign sugars no harm will ensue. However, if the sucrose or sorbitol does not produce a secretion of urine, it remains in the blood stream and in the body and interferes with normal metabolism.

For example, an eclamptic patient was given 200 c.c. of a 50 per cent sucrose solution intravenously. The urinary output averaged 100 c.c. per hour, but the blood chlorides, which were 512 mg. per cent before the injection, were 244 mg. per cent four hours after the injection. The blood sugar at this time after hydrolysis was still 234 mg. per cent. A similar injection of sucrose was given, and the patient died one hour later.

We have given 200 c.c. of a 50 per cent sucrose solution to five other toxemic patients, and in all of them the depression of the plasma chlorides was greater and lasted longer than after the administration of glucose, despite the fact that the osmotic pressure of sucrose is one-half that of glucose. Such a prolonged and marked depression of the electrolyte concentration is dangerous to life, because it interferes with the normal metabolism of the erythrocyte and tissue cells. We have had no experience with sorbitol, but its action would be similar to that of sucrose. Furthermore, Lindberg, Wald, and Barker have demonstrated that an injection of sucrose in a dog resulted in albuminuria and hematuria, and that sections of the kidney showed changes ranging from scattered areas of hyperemia to actual hemorrhagic necrosis of the glomeruli and marked tubular degeneration. Therefore, if these foreign carbohydrates are administered, they should be used with caution, and then only to increase the output of urine from an already functioning kidney.

Acacia and gelatin solutions have been used to increase the blood volume, and acacia has been used by us to produce a diuresis. A number of fatalities have been reported following the injection of certain types of acacia solution. No report in the literature has included the manufacturer's name nor a description of the solution.

We studied one patient who died following an injection of a specially prepared electrolyte-free solution of acacia. The blood pressure decreased to the shock level, coma ensued, the urinary output was adequate, the blood became more concentrated, and the plasma fibrin, which was 0.69 per cent before the injection, was 0 per cent four hours later, and the blood failed to clot.

We know of a parallel case also resulting in death. The usual acacia solution is water-clear, but the solutions used in the above described cases were opalescent. We have recently studied a third patient who was given a commercially prepared solution of acacia, and about three hours later a blood transfusion was given. An oliguria resulted and, although the twenty-four-hour urinary output finally amounted to 2,500 c.c., the patient died, apparently from sepsis. Studdiford has reported several fatalities in which acacia was probably the cause. He does not mention the name of the manufacturer nor the type of solution used. We believe that acacia solution is indicated primarily in shock, and we would not hesitate to use a properly prepared solution if blood were not available.

A 4.3 per cent solution of sulphate has been injected intravenously in the treatment of anuria. We have mentioned our objections to electrolyte solutions where there is renal impairment.

CONCLUSIONS

Oliguria is defined by us as the excretion of less than 600 c.c. of urine within twenty-four hours, and anuria as the absence of urine for twelve or more hours. Either condition, if present, is a serious complication in patients with eclampsia and pre-eclampsia, dehydration, massive hemorrhages, and blood transfusion reactions.

Electrolyte solutions are indicated in patients with dehydration and massive hemorrhage, but are contraindicated in the other conditions.

Acacia, sucrose, and sorbitol solutions are contraindicated in patients with anuria or marked oliguria.

Intravenous injections of a 20 to a 50 per cent glucose solution in distilled water are ideal in the treatment of oliguria and anuria occurring in patients with eclampsia and pre-eclampsia, and after blood transfusion reactions.

Blood transfusion entails a mortality of 0.1 to 0.3 per cent. These deaths are presumably preventable if proper precautions are taken in the typing, matching, and transfusion of the blood.

Oliguria or anuria requires an early diagnosis and intensive treatment, because the longer the renal impairment is disregarded, the more difficult it is to promote a secretion of urine. The treatment comprises a carefully balanced intake and output. Chemical analyses of the blood for cell volume, nonprotein nitrogen and plasma chlorides are also of inestimable value as a guide in the treatment.

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DISCUSSION

DR. WILLIAM A. THOMAS (Abstract).—I have seen very few cases of anuria or oliguria which came from renal disease itself. Even in the most advanced disease where there is an inability to excrete solids we still may have a normal amount of urine. The criteria by which we determine renal damage are the failure of the kidneys to concentrate and to dilute. So in these cases we may still have a relatively correct amount of urine but the solids are low and the patient may go into uremia. On the other hand, in oliguria or a decreasing amount of urine with high specific gravity, we cannot possibly have renal damage. So with a specific gravity of 1.010 to 1.030 there is obviously no inability of the kidney to excrete solids. It is a lack of water for the kidneys.

The question of dehydration demands some consideration. Edema was recognized largely as a nonrenal condition. It is a condition in which there is an increased tissue thirst and increased movement of the metabolites into the tissues. There are two types of dehydration: one is simply a lack of water administered to the body, the other a loss of fluid from vomiting or diarrhea. This is not true dehydration. There is a clinical condition called dehydration which is the exact opposite of edema, the reverse movement of metabolites is present, and in this condition anuria is the end result. As these cases are examined, the tissues are dry and there is an inability to hold water. Whether you give water subcutaneously or intravenously, there is no absorption. It remains in the tissues in lumps or masses. When we talk about dehydration we must distinguish between these two. When dehydration is due to alkalosis and has been preceded by polyuria, we must give large quantities of salt and hydrochloric acid in an effort to make the patient edematous. The decreased renal output in oliguria and allied conditions is probably due to tissue disease; it is an inability to get water to the kidneys. The kidneys are not badly damaged. Recovery is prompt and restoration of function is rapid.

When Dr. Dieckmann says that the tissues are saturated with water and salt as long as there is oliguria or anuria, my belief is that the tissues are not saturated. They contain an excessive amount of water and salt and all of these materials are moving into the tissues, and consequently eventually a diuresis results.

The action of glucose obviously is to increase the osmotic pressure of the blood itself, which is frequently lowered by the loss of serum proteins and the loss of electrolytes. The lowering of this osmotic pressure is the result of more fluid going into the circulation than is absorbed. With hypertonic solution we get a temporary increase in osmotic pressure. I have never seen it measured as Dr. Dieckmann has shown. I agree with Dr. Dieckmann that it is a very dangerous procedure to give electrolytes in the presence of poor renal function. When they are retained in the body as foreign substances they frequently cause more trouble than the condition we are seeking to remedy. It is true in the toxemia of pregnancy, though we see it too in nephritics.

I am not sure about the filtration pressure of the urinary arterioles. It has been frequently said that when this pressure falls below 80 there is anuria. It seems to me that failure of the urinary secretion is not due so much to a lowered systolic pressure as it is to a diversion of the fluids in the tissues.

DR. W. J. DIECKMANN (closing).—I agree that glucose is not a panacea for all diseases. Other solutions must be used when indications arise for them. Whenever there is poor renal function, caution should be used in the administration of solutions containing electrolytes.

ENDOMETRIUM-LIKE MUCOSA LINING THE FALLOPIAN TUBE*

Its Origin, Differential Characteristics and Clinical Significance

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DEVELOPMENTAL abnormalities of the gross structure of the body, or its individual organs, so far as their form and function after maturity are concerned, invariably carry with them histologic, pathologic, and clinical factors of importance. Most of the gross defects in structure are well recognized and if not completely understood are at least familiar and their general implications can be evaluated. On the other hand, although they may or may not occur as frequently in the body as the grossly abnormal processes do, abnormal changes in cells or layers of cells are less often seen and are more difficult to understand. Furthermore, although tissue abnormalities do not always have the same pathologic and clinical import as gross changes unquestionably they must be regarded as biologically significant. The cellular and tissue changes that are concerned primarily with repair and regeneration, as well as those profound alterations in cellular architecture which are associated with tumor formation or those which Hansemann has designated as anaplasia, will be avoided in this consideration. To be more specific, the changes to which we wish to make particular reference are those designated as metaplasia and heteroplasia. The general patterns of these atypical cellular and

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tissue transformations are familiar to almost all, but as has been stated there is need for a better understanding of them though there is general acceptance of a variety of influences and factors that are in operation to alter the normal pattern. Pre-eminently among these factors and influences, the vitamins, the hormones, and irritation due to infection have established significance unless further experimental and clinical investigation prove to the contrary.

Assuming that the current meaning of the two closely related terms metaplasia and heteroplasia is acceptable, instances can be multiplied in which squamous metaplasia has been demonstrated in the cervical canal, the uterine cavity and the tubal lumen. Mucous glands in the vagina, patches of gastric mucosa in the esophagus, and pancreatic tissue in the gastrointestinal tract may be mentioned as well-known examples of heteroplasia.

Since the female genital tract is an important part of the background upon which the subject of this paper is focused, it may be advisable for a better understanding of its development and versatility to recall that the embryonic relationship of the coelomic epithelium to that of the Müllerian duct is a very intimate one. It follows that actually the lining of practically the entire female genital tract descends from the same parent tissue, that is the Müllerian epithelium. The knowledge of this fact will later facilitate the explanation of why an atypical finding, though very rarely observed, should not be considered as particularly strange or inexplicable.

These introductory remarks now lead us to consider one of those abnormal tissue changes which is very infrequently seen and seldom described, that is, the complete or partial lining of the oviduct by a mucosa identical to that lining the uterine cavity, the endometrium. In the experience afforded by the laboratory of the New York Lying-In Hospital since 1932, there have been two instances in which the Fallopian tube was found to be lined by endometrium-like mucosa. The finding was so striking in each case that it was thought to merit study from the point of view of its origin, differential characteristics, and clinical significance. In surveying the literature, it was soon realized that little or nothing could be obtained from English sources and that for the most part the subject had been considered chiefly by the German writers. Further appraisal of what had been written revealed that a study of this abnormality would have little inherent clinical value. However, a review of the theories of origin in addition to the fact that the phenomenon probably represents another link in the chain of those interesting instances in which the morphology and function of cells and tissues presumably are transformed by the influences of vitamins, hormones or irritation, seems to place it outside the bounds of a bare histologic curiosity and, therefore, to justify this presentation.

One wishes to point out that the replacement of typical tubal mucosa by endometrium-like mucosa must not be confused with such pathologic lesions as endometriosis, adenomyosis of the tube, salpingitis isthmica nodosa, and follicular salpingitis, even though it is possible

that the abnormality may overlap or may be directly or indirectly related to any of them. Furthermore, one should like to divorce the process from the conception that it is ectopic endometrium as suggested by the theories of Novak and Sampson. On the contrary, it should be treated as Robert Meyer does, namely as a mutation which occurs locally in the tubal mucosa, capable of reacting to hormonal changes even to the point of menstrual desquamation just as uterine mucosa does.

A Fallopian tube lined by endometrium instead of tubal mucosa was first noted by Webster in his monograph on *Ectopic Pregnancy,* published in 1896. He made the observation on the opposite tube in a woman operated upon for ectopic pregnancy. Since then, further observations and case reports have been recorded by Höhne, Schridde

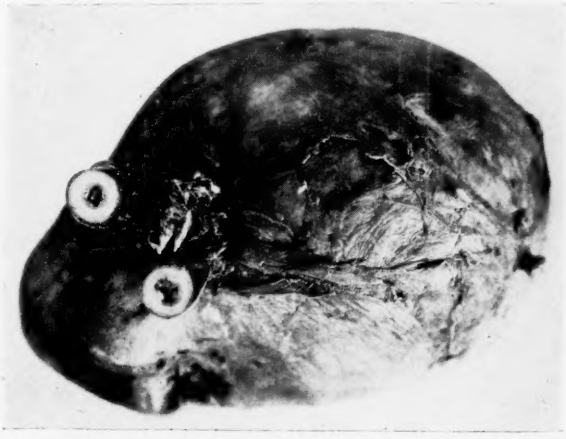

Fig. 1.—Case 1. Gross specimen illustrating the length and thickness of the affected Fallopian tube and the appearance of its cut surface.

and Schönholz, Schwarz and Crossen, Schindler, Mestitz, Lahm, Robert Meyer, Szamek, Cordua, Neumann, and most recently by Philipp and Huber. In this review and discussion, we wish to include the report of the two cases which came under our observation.

Case 1.—A. T. (Hist. No. 164222), a married negress, aged 37 years, had one child aged 15 years, was admitted to this clinic April 5, 1937, complaining of lower back pain of two years' duration and worse at the time of her menstrual periods. She was told by her family physician that she had "fibroids." Her past history was essentially negative. Especially important are the facts that she had no operations nor any history of pre-existing pelvic infection. The only irregularity in her menstrual history was the experiencing of dysmenorrhea for the past two years, during the first three days of her periods. Last menstrual period was March 16.

Except for an enlarged nodular uterus, physical examination was essentially negative. On April 7, 1937, a subtotal hysteromyomectomy, right salpingo-oophorectomy, and appendectomy were performed. The left tube and ovary, which appeared normal, were allowed to remain in situ.

The postoperative course was uncomplicated and to date has been asymptomatic and satisfactory.

Pathology.—The specimen consisted of a myomatous uterus with the right tube and ovary attached to it, the ovary being about normal in size and appearance. The tube was 4 cm. long, of fibrous consistency, and the normal convolutions were found wanting. The distal half was thickened measuring about 1 cm. in

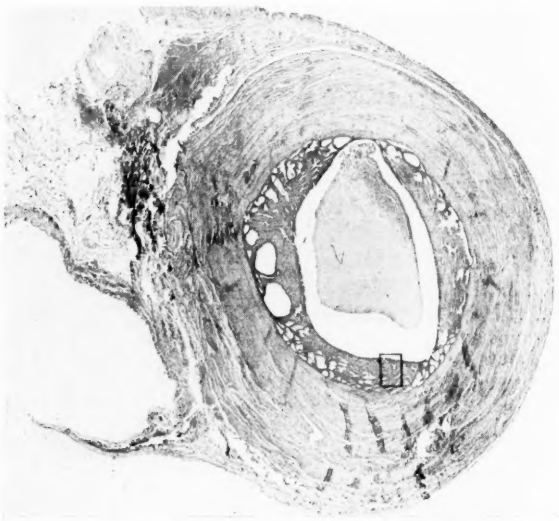

Fig. 2.—Case 1. Cross section of the Fallopian tube, demonstrating the endometrium-like mucosa lining the lumen. ×10.

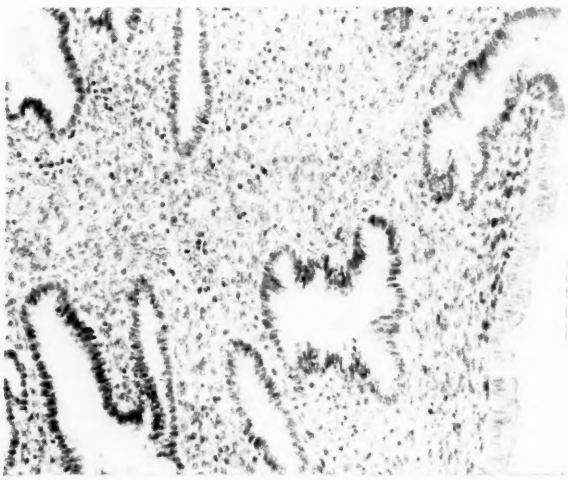

Fig. 3.—Case 1. A high power magnification of an area in the mucosa in Fig. 2, showing its similarity to the endometrium (see Fig. 4) and corresponding to the secretory phase. ×240.

diameter at its widest portion, the fimbriated end was sealed and smooth. Anatomic relationships were accurately established to exclude the possibility of a rudimentary horn of a bicornuate uterus.

Microscopic examination of the uterine tumor revealed a typical myoma, undergoing hyaline degeneration. The ovary included a corpus luteum and was devoid of abnormal findings. The endometrium was in the secretory phase.

Cross section through the Fallopian tube taken at the point of maximum thickness showed the following striking changes: The serosal surface as a whole was intact and smooth. The muscular wall was thickened by a hyperplasia of the circular muscle fibers. The lumen was almost pear-shaped and lined by a mucosa identical to the endometrium. The glands, for the most part, were tortuous, lined by columnar epithelium with central to basal nuclei and the individual cells showed evidences of secretion. The glands were also embedded in a cellular connective tissue stroma whose cells were round to ovoid. There was a slight degree of leucocytic infiltration in the stroma. Thus the composition of this mucosa was not unlike that lining the uterine cavity and functionally demonstrated unmistakable hormonal response to the corpus luteum. The absence of any tendency to form mucosal folds was thought noteworthy. The line of demarcation between the mucosa and muscularis was regular and rather sharp.

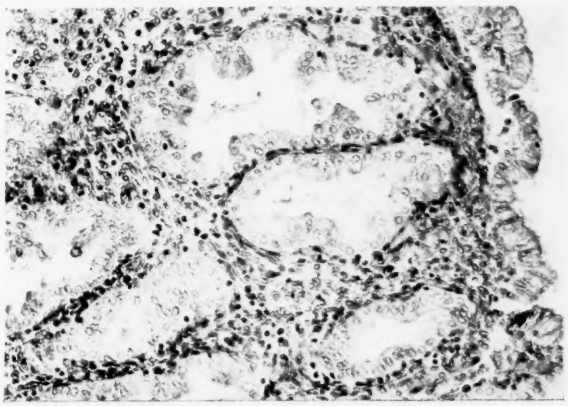

Fig. 4.—Case 1. A high power magnification of an area in the endometrium (uterus) in the secretory phase. ×240.

Because of the findings in the routine section of the oviduct as described above, serial sections were cut for study and special stains to include examples from all parts of it. It was learned that the abnormality involved the distal half of the tube and that the proximal half showed the gradual transition and connection of the interstitial portion to the cornual portion of the endometrial cavity. Special care and interest were taken in this general area to exclude the presence of adenomyosis.

Diagnosis.—Myoma uteri, normal premenstrual endometrium, normal ovary with corpus luteum, normal appendix, Fallopian tube lined by endometrium-like mucosa (premenstrual phase).

Case 2.—M. H. (Hist. No. 193773), a married white woman, aged 36 years, had one child aged 7 years, was admitted to the hospital Feb. 3, 1937, complaining of pain in the left lower quadrant of six months' duration. She had an attack of pain in the "left ovary" fifteen years ago, at which time she was confined to bed for a period of three weeks. There had been no irregularities in her menstrual history. Last menstrual period was Jan. 11, 1937.

Following routine physical examination, a laparotomy was advised for bilateral adnexal masses. On Feb. 3, 1937, the abdomen was opened. The uterus appeared normal. A multilocular cystic mass about 10 cm. was found in the region of the right ovary; a thick-walled cystic mass about 6 cm. in diameter replaced the left ovary. The uterus, both tubes and both ovarian masses, and the appendix were removed. Convalescence and follow-up were satisfactory.

Pathology.—The uterus was not remarkable. The capsules of both ovarian cystic structures were thick and the internal surfaces were covered by a thick chocolate colored hemorrhagic exudate. The left tube was 3.5 cm. long and about 0.75 cm. in diameter, the fimbriated end was sealed and smooth, no convolutions were

noted, the wall was fibrous in consistency. The right tube except for being roughened by adhesions appeared normal.

Microscopic examination revealed a normal myometrium and endometrium which was in the secretory phase. The sections of the ovarian cysts showed the characteristic evidences of endometriosis. Histologically the right tube was normal. A section through the left tube revealed a serosal surface whose regular and smooth contour was broken by adherent tags of organized connective tissue. The muscular layers were hyperplastic. The lumen of the tube tended to be rectangular in shape and was partially filled with a pinkish exudate containing a moderate amount of degenerated blood cells. The normal lining of the tubal lumen was replaced by an endometrium-like mucosa in the secretory phase. The histologic characteristics and details of this mucosa were like those described in the previous case. Once more serial sections were studied. The process in this Fallopian tube was found more extensive inasmuch as it involved the distal two-thirds of its length as compared to the distal half in the first case. Extension of the ovarian endometriosis to any part of the tubal wall was lacking, as well as any evidence of adenomyosis.

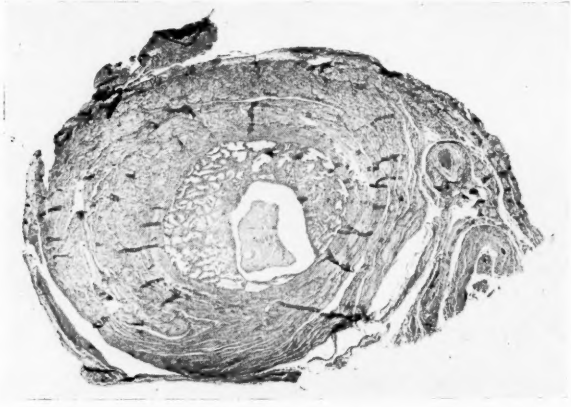

Fig. 5.—Case 2. Cross section illustrating the replacement of typical tubal mucosa by an endometrium-like mucosa in the secretory phase. ×10.

Diagnosis.—Normal uterus with secretory endometrium, bilateral endometrial cysts of the ovaries, normal right tube, normal appendix, left tube lined by endometrium-like mucosa (secretory phase).

THEORIES OF ORIGIN

The thought advanced to explain the origin of this unique finding in the Fallopian tube may be divided into two general categories; one supports the theory that the abnormality is the result of a congenital anomaly, and the other builds its argument upon the presence of a congenital anlage from which a heteroplastic change may develop only after a stimulating factor has been released to react upon the anlage.

The writers who chiefly support a theory with a congenital anomaly as its background are Webster, Schridde and Schönholz, and Schindler. Now, Neumann points out that there is a considerable difference between congenital anomaly and congenital anlage. In order that some abnormality or change can be considered a congenital anomaly, it must be present at birth, hence one should be able to see it in the fetus and in the newborn. Neumann pursued embryologic studies upon the course of the development of the Müllerian ducts up to the formation of the finished tube, and they failed to reveal the existence of any such mal-

formation, for he always found an open canal, never the rudiment of a diverticulum nor the fusion of tubal mucosal folds. The same negative results were realized when he completed a careful examination of 45 pairs of oviducts obtained from newborn full-term females. Robert Meyer's investigation of 300 Fallopian tubes likewise failed to show any congenital anomalies referable to the mucosa. It appears that the studies of Neumann and Meyer conclusively point to the fact that congenital malformations in the oviduct, according to the conception of Schridde and Schönholz, remain to be proved. Neumann is also of the opinion that the so-called "cytogene" or reticular tissue, to which Schridde and Schönholz refer, belongs to the normal course of development of the tubes, and with Lahm is agreed that it bears no relationship whatever to the "cytogene" tissue or stroma in the endometrium of the adult woman, and consequently cannot be offered as proof to uphold Schridde and Schönholz' theory of dysontogenesis.

Lahm believes in a congenital change but only in the sense that it is the outcome of a congenital lack of differentiation of the tubal mucosa whose source is a congenital anlage. The unfolding of this process into atypical mucosa, he proposes, is primarily dependent upon a particular stimulus, and the stimulus is initiated by the impulse of the ovarian hormones in the sexually mature woman. He definitely feels that the abnormality is not the result of an inflammatory process.

Robert Meyer attributes the finding of endometrium-like mucosa in the tube to heteroplasia. He feels that one should not wonder at such an intricate misplaced tissue differentiation in the oviduct when one stops to consider the fact that the lining of practically the entire female genital tract is derived from the Müllerian epithelium. He states boldly that it would be a distinct source of wonderment if endometrium could not be formed on the tube. It is reasonable to suppose then that there are especially suited cells lining the tubal lumen which may undergo misplaced differentiation, in other words, a congenital anlage lending itself to heteroplasia and indicating that the cell or group of cells constituting it is in possession of a dormant multipotent biologic capacity. Such indifferent cells must be aroused to development or proliferation as soon as they are affected by stimulus-releasing factors. When these particular cells give expression to their dormant capacity, it is clear that they can become an efficient functioning mucosa like the endometrium only in the presence of normal ovarian function. While Meyer believes that there is no unusual mucosal structure in the tube that inflammation cannot reproduce, it seems plausible to infer that the particular finding presented in this discussion can occur without having been preceded or initiated by an inflammatory process.

In the light of what has been advanced, there is sufficient evidence to make it appear that endometrium-like mucosa in the tube is unquestionably of postfetal origin and not the result of a congenital anomaly. Furthermore, Robert Meyer's theory of heteroplasia explains better than any other the process of its development, irrespective of the nature of the stimulus that initiates it.

DIFFERENTIAL CHARACTERISTICS

From the small number of cases that have been reported in the literature, it is clear that endometrium-like mucosa can exist in the tube without an associated lesion, such as salpingitis isthmica nodosa, adenomyosis, endometriosis, or follicular salpingitis. These pathologic processes are particularly mentioned because, at times, they may overlap or may even be confused with the atypical mucosal finding in the tube. For the purpose of contrast, it will be necessary to present

briefly the histologic picture and characteristics of the tubal abnormality, and then make some short comment as it is compared to the other lesions.

From the examination of the two specimens reported in this presentation, in addition to the others described in the literature, in general one may say that the Fallopian tube is usually thickened, may or may not have a bulbous enlargement along its course, is devoid of convolutions, the fimbriated end is usually sealed and smooth, and the altered mucosa may line the entire length of the lumen or only a part of it. Microscopically, the mucosa is found to be identical to the endometrium, and the ovarian hormones influence the function of the mucosa as if it were in the uterine cavity. The line of demarcation between the mucosa and muscularis is rather sharp and regular. The circular layer of muscle fibers, as well as the longitudinal, may be hyperplastic. Serial sections in our cases failed to reveal any epithelial spaces in the outer and middle layers of the musculature. Finally, any attempt on the part of the mucosa to form folds is not in evidence.

For comparison, let us first consider salpingitis isthmica nodosa and follicular salpingitis. It is generally agreed that the responsible agent for these lesions is always an inflammatory one, most frequently the gonococcus. One only needs to recall the pathologic picture of these two lesions, and by comparison it will be concluded that they bear no relationship to the tubal abnormality under consideration.

A pathologic process in many respects not unlike salpingitis isthmica nodosa, but which has nothing to do with it, is adenomyosis of the tube. It is a lesion which appears in the sexually mature woman and is characterized by nodular thickening only in the isthmic and interstitial portions of the tube. It is an example of heterotopic infiltrative proliferation of the mucosa, but unlike salpingitis isthmica nodosa occurs without proved pre-existing inflammation. This, without proved inflammation, must originate under conditions similar to its occurrence in the uterus. Two possibilities are offered for its origin in the tube: (1) transmission or continuation of uterine adenomyosis, (2) heteroplasia according to the theory of Robert Meyer. If one considers the second genesis, it is remotely possible that endometrium-like mucosa in the tube could be a forerunner of tubal adenomyosis.

Two points of special interest may be deliberated when endometrial mucosa in the tube is treated in relation to endometriosis. That it is a consequence of endometriosis is conceivable only so far as it is found in association with it in the sense that the stimulus which would cause the endometriotic process elsewhere, be it hormonal or inflammatory or both, might be the same factor responsible for the formation of the atypical mucosa in the tube. That it may be the cause of endometriosis in the pelvis has already been considered by Schindler and more recently by Philipp and Huber. If, according to their conception, such a membrane in the tube functions as in the uterus, then it seems reasonable to suppose that viable fragments could find their way through

the tubal lumen into the peritoneal cavity and there implant themselves to be the origin of endometriosis.

CLINICAL SIGNIFICANCE

Any conclusive or generalized statements relative to its clinical significance are prohibited because the cases are too few and the abnormality too rarely observed. However, most authors are in agreement that it may predispose the woman to ectopic pregnancy. Another consequence may be the development of a hematosalpinx as a result of tubal menstruation (cases of Lahm, Neumann, Meyer and Schindler). Should a hematosalpinx develop, it may become sufficiently symptomatic to be the cause of a real dysmenorrhea, as the cases of Meyer and Schindler clearly demonstrated. Finally, it is conceivable that the tubes bearing this abnormality may dispose the individual to sterility, since the fimbriated ends are usually sealed.

SUMMARY

1. The formation of endometrium-like mucosa in the Fallopian tube is a tissue abnormality which is infrequently seen and seldom described. It responds to the ovarian hormones in its functional activity, just as the endometrium does even to the point of menstrual desquamation.

2. Two cases with clinical and histopathologic findings are reported.

3. The theories of origin are briefly reviewed, and it is concluded that Robert Meyer's theory of heteroplasia explains better than any other the process of its development.

4. The differential characteristics are enumerated and contrasted with several pathologic lesions of the tube.

5. Endometrium-like mucosa in the tube carries little clinical value. Interest centers chiefly upon its biologic significance.

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DISCUSSION

DR. MORRIS A. GOLDBERGER.—The epithelium of the Fallopian tube may be the origin of this displaced or misplaced endometrium. This may be either pre- or postnatal. The postnatal origin is probably on the basis of inflammation with its concomitant proliferation and heterotopy. The epithelium of the uterus can invade the tubal wall by direct extension from the uterine cavity, or, according to Sampson, it may be transported in the course of retrograde menstruation with implantation in the tubal wall. Also, according to Sampson, rupture of an endometrial cyst with secondary invasion into the tube, may occur such as Dr. Marchetti noted in his second case.

Lymphogenic transportation of endometrium into the tube (Halban's theory) is not generally accepted, because endometrial tissue is never found in the regional glands and the endometrial particles are usually larger than the lymph stream can carry.

The seroepithelial genesis of endometriosis can occur by proliferation of serosal endothelium into the tube wall. We know that the pelvic serosal cells can respond to decidual changes.

Congenital epithelial anomalies may arise from Mueller's ducts, from the Wolffian body, or primordial kidney. This is stressed by von Recklinghausen, who found glomerular-like and secretory ductlike formations in the endometrium of the tube. The Wolffian duct and serosal endothelium have also been cited in fetal endometriosis.

These theories throw some light on the epithelial component, but there are still the stroma and the muscular elements, the origin of which, even hypothetically, is unknown. Sampson's theory, which is the most accepted one today, does not explain the formation of the cytogenic stroma in endometriosis. We know that epithelium can be transported or transplanted experimentally, but the stroma cells are very perishable and undergo rapid necrobiosis. This is commonly seen in menstrual endometrial casts.

It may be assumed that the cytogenic tissue in uterine endometriosis arises in the uterine mucosa. In tubal endometriosis, it may be the tubal mucosa or the intermuscular connective tissue which forms the cellular mantle in which the epithelial cells lie. This twofold origin of the stroma in endometriosis might explain some of the histologic pictures, because there are instances in which there is typical cytogenic stroma, and others in which a fibrillar connective tissue surrounds the epithelium and glands.

DR. ELIOT BISHOP.—The presence of endometrium-like mucosa in the Fallopian tube is connected in my belief with the occurrence of pregnancy after tubal ligation. Lutz, of the Peck Memorial Hospital in Brooklyn, has reported a case of ectopic pregnancy following the Madlener operation. Rubovitz and Kobac (*American Journal of Obstetrics and Gynecology* **27**: 12, 1934) reported two cases of pregnancy after the original Madlener technique. Their sections seemed to show that there was tunneling of the endosalpinx which had probably undergone endometrial changes. Sampson (*American Journal of Obstetrics and Gynecology* **20**: 443, 1930) has described "post-salpingectomy endosalpingiosis." This explains the rare cases of pregnancy after an operation on the Fallopian tube.

DR. HERBERT F. TRAUT.—The embryologic origin of all the epithelia of the female genital tract is identical in that they originate from celomic epithelium. Through occasional lack of differentiation or because of abnormal stimuli during periods of differentiation, we get histologic admixtures of apparently misplaced epithelial cells. Thus, we commonly see squamous changes among the cylindrical cells of the cervical glands as well as among those of the endometrium. Mucous cells similar to those of the cervix are sometimes found in the endometrium. On the other hand, it is not uncommon to find the peritoneum of the pelvis forming cells which simulate those of the endometrium and endosalpinx. This demonstration of Dr. Marchetti in which he definitely shows that the endosalpingeal epithelium may occasionally differentiate in the direction of endometrial mucosa instead of the usual type, while not of great clinical significance, is of importance, because it shows that all parts of the genital tract can undergo these mutations.

DR. WILLIAM LATZKO (by invitation).—I shall discuss only one feature of Dr. Marchetti's paper, namely, the manner in which the endometrium finds its way into the tube. The most generally accepted theories are:

1. R. Meyer's theory of heteroplasia, by abnormal differentiation of indifferent cells or of not yet fully differentiated cells;

2. The metaplastic theory of postfetal change of the mucosa of the Fallopian tube to endometrium.

My remarks will refer chiefly to the last mentioned theory. Caffier and others have doubted the possibility of metaplastic change of totally differentiated cells. Yet certain observations show us that Caffier's objections are not essential: (a) We find an extraordinary instability and variability of the endometrium at the time of puberty. (b) Furthermore, the endometrium and mucosa of the tube are both derivatives of the same tissue, namely the celom, as Russel pointed out as early as the year 1899. (c) Finally several authors (Franqué, Mahle and McCarthy, Lemon and Mahle, Sampson) have asserted that endometrioma of the tubes originates from the tubal mucosa. (d) It is interesting also to recall a most interesting communication of Morau who, in 1891, observed in the pig, dog, cat, and mouse the transformation of the peritoneal epithelium under the influence of rut first into embryonal, afterwards into ciliated, epithelium. In conclusion, it may be definitely stated that tissue descending from the celom is able to change its character in postfetal life. We may ask therefore why it is so difficult to suppose a postfetal transformation of tubal mucosa to endometrium.

There exists also, however, a real proof of metaplasia. I refer to clinical experiences with an operation described by Strassmann for cases of amenorrhea due to total or almost total loss of endometrium as a result of excessive curettage, severe puerperal infection or tuberculosis of the uterus. In this operation Strassmann made a hole through the uterus in the direction of its axis and introduced a tube, left in connection with the broad ligament, into the new formed uterine canal. Now the tube lay with its ampullar extremity opening into the peritoneal cavity and the uterine end projecting into the vagina. Strassmann performed that ingenious operation six times. With a similar operative technique devised to avoid amenorrhea after subtotal hysterectomy, Fuchs operated seven times. In these 13 patients regular menstruation continued. Moreover one of Strassmann's patients became pregnant and gave birth at full term to a normal child. That proves almost with certainty that the Fallopian tube can assume such functions of the uterus as menstruation, formation of decidua, and support of pregnancy to its normal termination. So we can state with a probability near to certainty, that in these cases the tubal mucosa was changed into endometrium.

PROLAPSE OF THE UMBILICAL CORD*

An Analysis of 58 Cases

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PROLAPSE of the umbilical cord is an infrequent complication of labor, which becomes significant because of the resultant high fetal mortality rate and the employment of radial operative procedures that increase the maternal hazard. Little is known about its etiology except that conditions which interfere with the proper filling of the pelvic cavity by the presenting part conduce to its development. This study was undertaken to ascertain whether any other factor, possibly nonpreventable in character, could be recognized as favoring funic prolapse.

MATERIAL

Among 9,546 deliveries at the University Hospitals between July 1, 1926, and Dec. 31, 1939, there were 63 prolapsed cords, an incidence of 1:152, or 0.66 per

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cent. Five cases involving previable infants (birth weight less than 1,500 Gm.) were excluded from the analysis, making a corrected incidence of 1:164, or 0.61 per cent. Forty-nine of the children weighed 2,500 or more grams at birth and 9 weighed between 1,500 and 2,499 Gm. Twenty cords prolapsed into the vagina and 38 appeared at the vulva.

The series included 23 primigravidas and 35 multigravidas whose obstetric histories presented no unusual features and no records of similar accidents. Abnormal pelves (simple flat, 1; typical funnel, 3) were recognized in 4 women, an incidence of 6.9 per cent. There were 2 twin pregnancies, but in each instance the cord of the second child did not prolapse. There were 2 marginal placenta previas and 5 toxemias of late pregnancy, necessitating the induction of labor. Three children showed compound presentations, in contrast to the usual incidence of approximately 1:250.

The Voorhees bag was used 7 times, twice in conjunction with the cord shield, 3 times in attempts to maintain the cord within the uterine cavity after replacement, and twice for incidental obstetric complications. Artificial rupture of membranes was performed 21 times, in 14 instances for the induction of labor and in 7 after complete cervical dilatation.

MORTALITY RATES

Twenty-seven of the 58 babies did not survive, a mortality rate of 46.6 per cent. Among the 49 term babies there were 20 deaths (40.8 per cent) and among the 9 premature infants 7 deaths (77.7 per cent). Four patients were admitted with prolapsed cords, but none of the children survived, although 2 of the cords were pulsating feebly at admission.

The 27 fetal deaths were studied with relation to the parity of the mother, the station of the presenting part, the dilatation of the cervix at the time of prolapse, the fetal presentation, and the type of delivery.

Parity.—The fetal mortality rate among the primigravidas was 60.9 per cent and among the multigravidas 37.2 per cent. The higher rate in the former is undoubtedly related to the longer labors and to the greater difficulty of operative deliveries.

Station.—As might be expected, the higher stations of the head were associated with increased fetal mortality rates (Table I). When the presenting part was not engaged, or floating, the death risk was 75 per cent greater (66.6 per cent) than when the presenting part was below the spines (37.5 per cent).

TABLE I. FETAL MORTALITY RATES VERSUS STATION OF PRESENTING PART AT THE TIME OF PROLAPSE

	CEPHALIC		BREECH		TRANSVERSE		TOTAL		
								DEAD	
	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD	ALIVE	NO.	PER CENT
Not engaged	2	3	0	2	2	3	4	8	66.6
At or above the spines	9	10	8	3	–	–	17	13	43.4
Below spines	6	4	4	2	–	–	10	6	37.5

Note the decrease in fetal mortality rate with the descent of the presenting part in the pelvis.

Cervical Dilatation.—The chance for fetal survival was also diminished when the prolapse occurred through an incompletely dilated cervix (Table II). With complete cervical dilatation, the fetal mortality rate (36.7 per cent) was not quite 60 per cent as great as when the cervix was less than 5 cm. dilated (63.8 per cent).

Presentation.—Fetal position likewise influenced fetal survival, with the lowest death rate in breech and the highest in transverse presentations. It is curious, as Kurzrock[1] has indicated, that the fetal death rate is relatively high in transverse presentations where the possibility of serious cord compression would seem to be minimal. Possibly the fact that in such cases the cord prolapses through an incompletely dilated cervix and that rapid delivery by version and extraction is commonly employed may explain the poor results.

TABLE II. FETAL DEATH VERSUS DILATATION OF CERVIX AT THE TIME OF PROLAPSE
FETAL DEATH VERSUS PRESENTATION

	CEPHALIC		BREECH		TRANSVERSE		TOTAL		
								DEAD	
	ALIVE	DEAD	ALIVE	DEAD	ALIVE	DEAD	ALIVE	NO.	PER CENT
5 cm. or less	3	6	1	4	1	1	5	11	63.8
More than 5 to 10 cm.	2	3	4	1	1	1	7	5	41.7
10 cm. or more	12	8	7	2	0	1	19	11	36.7
Totals	17	17	12	7	2	3	31	27	46.6

Note the decrease in fetal mortality rate with the increase in size of the cervix.

ETIOLOGY

Many theories concerning the etiology of funic prolapse have been advanced, but none offers a completely satisfying explanation. Since no cord can prolapse into a pelvis which is adequately filled by the presenting part, nor descend from an intact amniotic sac, any circumstance which: (1) produces maladaptation of the presenting part to the pelvis (malposition of baby, contracted pelvis, tumors, etc.), (2) dislodges an engaged presenting part (insertion of bag, pelvic examination), or (3) produces early rupture of membranes, has been considered etiologically significant. Moreover, a few authors have suggested that the chance occurrence of an abnormally long funis may be important. Each of these theories will be discussed.

Maladaptation.—With a normal pelvis and a normal size baby, an engaged head should fill the available space in the pelvic basin, whereas a breech would fill it less completely. With transverse presentations, on the other hand, the baby does not adapt itself to the pelvis until comparatively late in labor. In confirmation of these opinions there were prolapsed cords in 34 of 9,092 cephalic, 19 of 419 breech, and 5 of 35 transverse presentations, with percentage incidences of 0.37, 4.54, and 14.27, respectively.

In the present series there were 4 (6.9 per cent) contracted pelves, as against an incidence of 3.65 per cent in 4,144 Iowa women.[2] However, there was but one inlet contraction, and funnel pelvis is probably not involved in the etiology of prolapsed funis.

Dislodgment of Presenting Part.—Upward displacement of the presenting part may occur during the conduct of labor, as in the introduction of a Voorhees bag or at premature rupture of the membranes, and may precipitate funic prolapse. The bag was employed twice for incidental obstetric complications, placenta previa and delayed cervical dilatation, and in each instance the cord prolapsed as soon as the bag was removed. On the other hand, the bag is frequently employed without the occurrence of prolapse. Moreover, the accident occurred in five cases immediately after the artificial rupture of the bag of waters.

Rupture of the Membranes.—Prolapse of the cord cannot occur with an intact amniotic sac, even though funic presentations may appear before the membranes are ruptured and thus predispose to prolapse. Except in these latter cases, it is not reasonable to assume that rupture of the bag of waters is the sole cause of prolapse of the cord even though it does immediately precede the accident. In 14 cases, premature artificial rupture of the membranes preceded the prolapse. In 5 instances, the cord prolapsed immediately, while in the remaining 9 cases, the prolapse occurred from fifty minutes to thirteen hours later, suggesting the operation of some other factor.

These figures are confusing, but a study of 1,000 women in whom labor was induced electively by premature artificial rupture of the membranes[3] showed only 4 prolapsed cords, while a control series of 1,000 women who had spontaneous onset

of labor without artificial rupture of membranes also had 4 prolapsed cords. The first group was carefully selected with regard to bony pelvis and presentation to reduce the possibility of prolapsed cord. Nevertheless it is apparent that the complication should have appeared much more often if premature artificial rupture of the membranes is a significant factor in the etiology of prolapse of the funis.

Long Cord.—Since a prolapsed cord is *doubled* it must be of considerable length before the loop can appear at the vulva. The average length of 55 measured prolapsed cords was 73.0 cm. (Table III). Three cords were not measured. Since the accepted range of normal cord length is 25 to 75 cm., it is apparent that the average length of the 55 prolapsing cords was at the extreme upper limit of normal. It is felt that chance alone could not account for this finding.

Apparently prematurity was not a factor influencing cord length, since there was no significant difference between the average cord lengths of premature and of term-sized babies (Table III).

TABLE III. DISTRIBUTION AND AVERAGE OF PROLAPSED CORDS

CENTIMETERS	TERM NO.	PREMATURE NO.	TOTALS NO.
45-49	2	0	2
50-59	3	1	4
60-69	11	4	15
70-79	14	2	16
80-89	12	0	12
90-99	3	1	4
100-109	1	1	2
Totals	46	9	55
Average Length	73.2 cm.	72.1 cm.	73.0 cm.

The lengths of the cords less than 60 cm. were: 45, 49, 50, 56, 56, 57.

Note that prolapsing cords tend to have an average length at the extreme upper limit of normal, and that there is no significant difference between the average lengths of cords of term and of premature babies.

The average cord length of the 5 abortions was 62.0 cm.

Only 6 prolapsed cords were less than 60 cm. in length. A detailed analysis of these cases was undertaken to ascertain if there were any special features contributing to the prolapse. In 4 the funis prolapsed into the vagina but did not appear externally, possibly because the cord was not sufficiently long. There was no evidence in any of the 6 to indicate that low placental implantation contributed to increase of the effective cord length but the possibility cannot be eliminated. No other etiologic factor was revealed.

Believing that abnormal cord length may play a more important part in causing prolapse of the funis than has generally been recognized, an analysis of patients with prolapsing as well as those with nonprolapsing cords 75 or more centimeters long was undertaken. There were 545 such umbilical cords of which 20 prolapsed and 525 did not.

The influence of the long cord is shown in Table IV. If, in addition to recognized etiologic factors, a long cord is present, the danger of prolapse of the funis is strikingly increased. Prolapse among the long cords occurred with a frequency *6 times greater* than that among the entire series of 9,546 deliveries. This suggests that the long cord is a definite and important factor in the etiology of prolapse of the funis.

While the danger of funic prolapse is moderate when there is maladaptation of the presenting part to the pelvic inlet, as in breech and transverse, it is much greater when the umbilical cord is 75 or more centimeters in length. As a corollary, one may assume that the danger of a funic prolapse in breech and transverse presentations is comparatively slight if the cord is of average length, but becomes increasingly serious with longer cords.

Nonprolapsing Long Cords.—In order to determine the probable reasons for the failure of prolapse of the 525 long cords each of the case records was analyzed.

TABLE IV. INCIDENCE OF PROLAPSE, IN GENERAL AND AMONG PATIENTS WITH CORDS MEASURING 75 OR MORE CENTIMETERS

	ENTIRE OBSTETRIC SERVICE			PATIENTS WITH LONG CORDS		
	DELIVERIES	PROLAPSE OF FUNIS		DELIVERIES	PROLAPSE OF FUNIS	
	NO.	NO.	PER CENT	NO.	NO.	PER CENT
Cephalic	9092	34	0.37	509	9	1.8
Breech	419	19	4.54	33	9	37.5
Transverse	35	5	14.27	3	2	66.6
Totals	9546	58	0.61	545	20	3.7

Note the striking increase in the percentage incidence of prolapse in each position with long cord.

The frequency of prolapse among patients with long cords was 6 *times* greater than among the entire obstetric service.

Between July 1, 1926 and Dec. 31, 1937 among 7,874 women, there were 525 instances of nonprolapsing cords, measuring 75 or more centimeters. The incidence of long cord without prolapse was, therefore, 6.17 per cent, or 1:15. Repetition of the long cord was observed twice in 18 women, three times in 4, and five times in 1.

There were 500 cephalic, 24 breech, and 1 transverse presentations in this series. There was no patient with inlet contraction, so that the presenting part was free to enter the pelvis in each instance. The usual factors influencing prolapse, notably maladaptation, were conspicuously absent. Furthermore, in complete or single footling breech presentations where prolapse might commonly be expected, adventitious factors, such as coils of cord around the neck, tended to prevent it.

It seems reasonable to assume that maladaptation of the presenting part to the pelvis was absent in the 500 vertex presentations in this series. In other words, the cord could not enter a completely full pelvis. Seventeen of the 24 breech presentations were of the frank variety and again an adequate filling of the pelvic inlet may be postulated. In each of the 3 patients with complete breech, and in 3 of 4 single footling presentations, the cord encircled the baby's neck one or more times. In the fourth single footling presentation, labor was precipitate, lasting only thirty-five minutes from onset until the legs and breech were born. It can be argued that with a longer labor, prolapse of the funis might have been encountered. In the one instance of transverse presentation, an arm prolapsed when the cervix was 3 cm. dilated, and it may be there was no room for the cord between arm and cervix.

It seems possible, therefore, to find a more or less adequate explanation for the failure of the long cord to prolapse in each of these 525 instances.

THERAPY

It is essential to remember that treatment for prolapsed cord is of importance only if the baby is alive. A physician recently brought a parturient primigravida to the Hospital with the story that a foot of a pulseless loop of cord had been hanging between her thighs for some hours. He was greatly disturbed when cesarean section was not performed.

Whenever the station of the presenting part and the condition of the cervix permit, immediate vaginal delivery is indicated. It must, however, be remembered that the child may die, not as a result of the prolapse, but from the operative procedure itself (Table V).

If conditions will not permit vaginal delivery without undue risk to the mother, recourse may be had to: (1) replacement, (2) the cord shield, (3) cesarean section, (4) acceptance of an unfortunate circumstance.

Replacement of the cord was attempted 4 times but could be accomplished only twice. One of these patients was a gravida xi whose cervix was half dilated. It

became sufficiently dilated during the vaginal manipulations to permit breech extraction of a living baby. The other unsuccessful attempt involved a gravida i whose cervix was half dilated when prolapse occurred and the baby subsequently was spontaneously stillborn. The cord was replaced and a bag inserted into two patients, both of whose babies were lost. It is of interest that the various operators avoided the use of replacement, since it was attempted but 4 times.

TABLE V. ASSOCIATION OF TYPE OF DELIVERY WITH FETAL DEATH

	ALIVE	DEAD	
	NO.	NO.	PER CENT
Craniotomy	0	1	100.0
Cesarean section	0	1	100.0
Low forceps	4	6	60.0
Midforceps	3	3	50.0
Breech extraction	12	9	42.8
Spontaneous delivery	3	2	40.0
Version and extraction	8	5	38.5
External version, breech extraction, manual dilatation	1	0	00.0
Total	31	27	46.0

Note that despite the known danger of version and extraction to the fetus, the operation sometimes was a life-saving measure.

Certainly the results were not good, and are in agreement with common teaching that replacement is little more than a gesture.

The cord shield was used twice, each time with fatal results to the baby. In the first case, previously reported,[4] the baby died from intracranial hemorrhage four hours and twenty minutes after breech extraction. The second patient was admitted with a pulsating cord prolapsed through a cervix 2 cm. dilated. The baby died in utero, but it is felt that with more experience in the use of the shield it might have been saved. Despite these poor results the shield may be of some value.

Cesarean section was not generally used, since it has not been considered justifiable to expose the mother to increased risk for a baby whose chances are so poor. The operation was performed once on a gravida iii at term, but not in labor. The cervix was 2 cm. dilated and the fetal heart was heard before the patient's abdomen was prepared. The baby, weighing 2.745 Gm., could not be resuscitated, and it was thought that the addition of an anesthetic agent to a partially asphyxiated baby was a fatal combination.

It is sometimes advisable for the sake of the mother to allow labor to progress normally without regard for the child. Especially when the cord has been compressed for a long time there is little justification for any radical operative attack.

Many bizarre and sometimes ludicrous incidents attended the deliveries. Under the pressure of circumstances absurd operations frequently were performed, sometimes with failure, sometimes with success. As a specific example, the baby of a gravida iii with a cervix 4 cm. dilated at the time of prolapse was saved by external version, manual dilatation and breech extraction. In another instance a gravida iv who was subjected to premature artificial rupture of the membranes when the cervix was 3 cm. dilated immediately pushed a loop of nonpulsating cord through the cervix. The fetal heart was audible and the patient was placed in an extreme Trendelenburg position. When labor started eighteen hours later the cord prolapsed to the vulva. Before and during the subsequent labor, which lasted three-and-one-fourth hours, the patient remained in extreme Trendelenburg position. When the cervix was 8 cm. dilated, version and extraction resulted in the birth of a 3,800 Gm. living baby. In one of the instances of prolapse with premature artificial rupture of the membranes, the patient was placed in extreme Trendelenburg position and anesthetized. The cord returned spontaneously to the uterine cavity and subsequently the head re-entered the pelvis. The cord did not prolapse again and a live baby was born spontaneously. Undue enthusiasm over two successes is not justifiable, but postural treatment may occasionally be of value.

SUMMARY AND CONCLUSIONS

1. Prolapse of the umbilical cord in the series of cases studied, occurred in 0.61 per cent of babies weighing 1,500 or more grams at birth, an incidence of 1:164.

2. The percentage incidence of prolapse among the various presentations was: cephalic 0.37, breech 4.54, transverse 14.27.

3. The fetal mortality rate was 46.6 per cent, but no mothers died.

4. The death rate of babies of primigravidas was almost twice that of babies of multigravidas.

5. The station of the presenting part at the time of prolapse influenced the fetal mortality rate as follows: at inlet 66.6 per cent, at midpelvis 43.4, at outlet 37.5.

6. The condition of the cervix at the time of prolapse influenced the fetal mortality rate as follows: Less than 5 cm. dilated 63.8 per cent, between 5 and 10 cm. 41.7, complete dilatation 36.7.

7. Premature artificial rupture of the membranes for the elective induction of labor did not influence the incidence of prolapse of the funis.

8. The average length of the prolapsed cords was 73.0 cm.

9. Among 545 patients with cords 75 or more centimeters long prolapse occurred with a frequency *6 times greater* than among the entire obstetric service.

10. The chance occurrence of a long cord is a prominent factor in the etiology of prolapse of the funis.

11. Treatment is inadequate. It is stressed that: (1) It is important only if the baby is alive, (2) undue jeopardy of the mother is not justifiable in view of the poor fetal prognosis.

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DISCUSSION

DR. DAVID S. HILLIS.—It appears from the comparison of Dr. Mengert's figures with the record of the Cook County Hospital that this accident occurs more frequently in Iowa than it does in Illinois. At the Cook County Hospital in 9,581 deliveries of viable infants, prolapse of the cord occurred only 25 times. Three patients were admitted with prolapsed cord in which the baby was already dead, so that if these be excluded from our series 22 cases are left to be considered. The total mortality among these cases was three babies, i.e., 13.6 per cent. One fetal death occurred in a primigravida and two in multigravidas. In 20 cases the pelvis was normal, in one case it was contracted, and in one case it was a justomajor pelvis. There were 11 breech cases, 10 cephalic cases, and one with transverse presentation. There were eight sets of twins and in these the prolapse occurred six times in the first twin and twice in the second. There were 15 floating heads at the time of prolapse, while in 3 cases the head was in midpelvis and in 4 below the spines. Cervical dilatation was less than 5 cm. in three cases, 5 cm. or over in four, and complete in 15 cases. Eighteen cords prolapsed at the time of rupture of the membranes, twice at the time of expulsion of the bag in placenta previa. One occurred twelve hours after rupture of the membranes, and one twenty-four hours after rupture. In 16 cases the bag of waters ruptured spontaneously, in six there was artificial rupture. In 10 cases of the 22 the bag of waters ruptured before entrance to the hospital.

The management of these cases was as follows: In one a Voorhees' bag was inserted after replacement of the cord, which was followed by spontaneous delivery of a live baby. Low forceps yielded a live baby in one case. In 9 cases there was an extraction of the breech with one death. Version and extraction was performed in three cases with one death. A Braxton Hicks' version was carried out in one case of placenta previa with loss of that baby. Spontaneous delivery occurred in four. The cord was replaced, Trendelenburg position used and breech extraction employed in one case; version and extraction and Dührssen's incision on 8 cm. cervix were undertaken in 1. Finally in 1 case spontaneous delivery followed the replacement of the cord, the pushing of the head into the pelvis and the Trendelenburg position.

The circumstances associated with the prolapse were these: Spontaneous rupture of the bag of waters in breech in seven cases; forelying cord and spontaneous rupture of bag of waters in 3; floating head, early spontaneous rupture of bag of waters in 3; artificial rupture for delivery of breech in 2; artificial rupture, insertion of bag and prolapse with expulsion of bag in 2; artificial rupture of bag of waters for bleeding in 2; membranes ruptured twelve hours, not in labor, prolapse at time of complete dilatation in 1; transverse presentation with ruptured bag of waters in 1; prolapse when head pushed up for manual rotation in 1.

The attending staff at Cook County Hospital is practically unanimous in the opinion that an intact bag of waters is a most valuable aid in the successful termination of labor, and the general policy of the clinic is to preserve the bag of waters until the cervix is completely dilated. Prevention of prolapse of the cord is only one of the reasons for this practice. Artificial rupture is performed only for the induction of labor in the most urgent cases, as in threatened eclampsia, and for the intraovular introduction of a bag or the treatment of marginal placenta previa.

In 14 cases, in the series reported, premature artificial rupture of the bag of waters preceded the prolapse, and in five instances, the cord prolapsed immediately after the bag of waters was ruptured. The question naturally arises, what would have happened to these 14 cases if the bag of waters had not been prematurely ruptured? Does the advantage expected from the artificial rupture of the bag of waters fully justify the risk?

DR. C. C. DRAA.—At the Presbyterian Hospital in Chicago during the last six years we have delivered 5,035 mothers, with the occurrence of prolapse of the cord in 18, giving us an incidence of 0.35 per cent as compared with Dr. Mengert's figure of 0.66 per cent. The etiologic factors in our series appeared to be a large baby, in six instances, and a contracted pelvis, in one instance. There were bag inductions in 3 cases and transverse presentations in 2 instances. There were 5 cases of breech presentations, and 2 twin pregnancies. The length of the cord was stated in only 3 cases in each of which it was noted to be abnormally long.

The method of treatment in our series was usually immediate delivery, because as a rule the cervix was completely or almost completely dilated. Version and extraction was resorted to in 10 cases; simple extraction of a breech presentation in 5 instances, and normal delivery occurred in 2 cases after replacing the cord. There was one forceps delivery.

The fetal mortality was quite interesting, in that the gross uncorrected mortality was 38 per cent. If we eliminate the previable babies the gross mortality was 22 per cent, which compares favorably with Dr. Mengert's series in which the gross fetal mortality corrected was 46.6 per cent. The main difference in the two series as we have tried to study them is first, the percentage incidence of prolapse of the cord, and second, the infant mortality.

Rupture of the membranes for induction of labor appears to be an important etiologic factor in producing prolapse of the cord. In Dr. Mengert's report of 58 cases of prolapsed cord, the membranes were ruptured artificially 21 times and yet one gathers the impression that he does not consider it of major etiologic importance.

Further as to fetal mortality it is obvious that the cord cannot prolapse until the membranes are ruptured, and second, the fetal mortality is lower with the greater dilatation present at the time of prolapse. So it seems that maintaining

the integrity of the membranes until they rupture spontaneously or until the cervix is sufficiently dilated that the descent of the head can be controlled so as to prevent prolapse of the cord is the better plan. As we have shown, practically all of our patients were deliverable at the time the membranes ruptured either artificially or spontaneously.

DR. RUDOLPH W. HOLMES.—There are two types of cord prolapse: one, the forelying cord before the membranes are ruptured, and the other the technical prolapse after the membranes have ruptured. In the former an exaggerated Trendelenburg position may cause a recession of the head from the inlet, will obviate the risks of funic compression, and may permit the cord to float upwards into the uterine cavity for the specific gravity is slightly higher than that of the liquor amnii. In the meanwhile, preparations may be made for the introduction of the bag *outside of the membranes,* the one place where such procedure is permissible. When such artificial dilatation has progressed sufficiently for the introduction of the hand, the hand should repose the cord, rupturing the membranes if they have fortunately withstood the bag pressure, and the cord hung over the buttocks and leg that it may not prolapse again.

After there is a true funic prolapse, the Trendelenburg posture is equally necessary in order that pressure may be diminished while preparations are being made for some other recourse: First, manual reposition if the dilatation permits it; if not, then the replacement by the method Dr. Cary employs may be successful at times, though forty years ago this method was discarded by myself on account of the difficulties and failures. Where conditions permitted it, I have always felt version was the one most likely to bring success, but under any circumstance fetal mortality necessarily must be high. I have never felt that cesarean section was indicated for this condition, for the danger of infection from drawing the prolapsed cord through the uterine incision is to be remembered. If a section be done, before the fetal extraction, the cord must be clamped at the navel, and cut: when the infant is delivered the cord must again be cut at the placenta, and the cord then extracted through the vagina. Cesarean section should not be recommended for general practitioners or general surgeons, the mortality being what it is.

DR. MENGERT (closing).—Dr. Hillis has stressed the low incidence of prolapse of the cord on the service with which he is connected and has implied that artificial rupture of the membranes had something to do with our high incidence. If we take out the 14 cases of premature artificial rupture from the 58 cases of prolapse, 44 instances remain, which still represents twice as many as on Dr. Hillis' service.

One of the main purposes of this paper was to discuss the long cord and to stress that it is a factor over which we have no control in the etiology of prolapse. Whatever one believes with regard to the benefit of an intact bag of waters during labor, I do not believe that its rupture is by any means the whole story or even a major part in the etiology of prolapse of the funis.

Dr. Draa has emphasized the comparatively low mortality rates at the Presbyterian Hospital. In reply, I might point out that most of our deliveries are done by students and rotating interns. The interns rotate two months on our service and are supervised by an assistant resident who is in the early years of his training. I think it is understandable that in the excitement of the moment operations are done which might be avoided by men of mature experience.

EPIDEMIC INFECTIOUS DIARRHEA OF THE NEWBORN INFANT*

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EARLY in September of 1938 a tragedy in the form of an epidemic of infectious diarrhea occurred in the overcrowded nursery of the Milwaukee Hospital. The epidemic was severe and many infants died, with discouragingly few recoveries. It was not checked until the maternity floor was closed and renovated.

Epidemic diarrhea of the newborn is a unique disease entity. Its clinical picture is that of a severe intestinal intoxication. It is accompanied by watery yellow stools, abnormal distention, precipitous loss of weight, drowsiness, marked dehydration, toxicity, and shock.

EPIDEMIOLOGY

The prevalence of this epidemic form of diarrheal disease among newborn infants is reflected in New York's infant mortality statistics. Frant and Abramson[2] show that although a satisfactory reduction has been evidenced in death rates from all causes among infants from one month to one year of age, an analysis of the vital statistics of New York City proves that little has been accomplished in effecting a suitable lowering of the death rates among infants in the neonatal period. In fact, as far as diarrheal deaths are concerned, the rate shows a steady ascent in mortality among newborn babies during recent years. Frant and Abramson attribute this increased mortality to the previously unrecognized clinical entity, namely epidemic diarrhea of the newborn infant. They have followed twenty-three outbreaks similar to our own in fifteen hospitals giving maternity care. From July, 1934 to July, 1937, they have followed the postnatal course of 4,594 live born babies. Among these, 711 cases, or 15.5 per cent, developed the disease. Nearly one-half or 335 of those infected died. The average mortality rate for the 4,594 babies studied was 7.3 per cent. In our own epidemic 39 infants, 31 full term and 8 prematures, were either in or entered the nursery subsequently to the onset of this epidemic. At that time or subsequently thereafter 22, or 56 per cent, became ill and 18, or 82 per cent, of this group died.

The following facts in regard to the disease have been found. It occurs during the first two or three weeks of life and attacks both sexes of any race or nationality. Older children and adults coming in contact with the affected infants do not contract the disease. On the other hand infants with very little acquired immunity are most susceptible to it. There is no relationship between the disease and the state of nutrition of the infant, although immaturity and prematurity lower the infant's resistance. The disorder has been recognized only in cities of the United States and countries lying within the North Temperate Zone.

In our epidemic, the probable source of infection was traced to the father of one of the deceased babies who visited the mother during a nursing period. At that time he was convalescing from an acute coryza and diarrhea. The baby on its sixth neonatal day, which was forty-eight hours following the father's visit, appeared ill, was immediately isolated with special nursing care, and it died in

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forty-eight hours. Because infectious diarrhea was suspected the entire obstetric floor was closed the same day and 23 apparently healthy babies discharged from the hospital while three infected ones were transferred to the pediatric department. Seven infants under isolation technique remained in the nursery.

During the following week 14 of the 23 infants who had been discharged were readmitted. All of these and the remaining 7 infants were isolated in private rooms with special nursing care and various pediatricians in attendance. The 7 mentioned above and 11 of the 14 readmitted infants contracted the disease and died.

According to the literature, no differences are evident in the frequency of the disease among either breast or artificially fed infants. This distinction is no longer so sharply defined because of the present practice of giving supplementary feedings to nearly all newborn infants. In our epidemic, 18 of 25 babies who were being fed on formulas, the day the obstetric floor was closed, died. All of these babies had been residents of the nursery for from three to twenty-eight days. The other 7 babies who did not contract the disease were in the case of two, inhabitants of the nursery for three days, one for two days, and the remaining 4 were born the day the nursery was closed. Six babies, ages seven to fourteen days, who received breast milk and one formula feeding, and 8 more, ages seven to eleven days, who obtained breast milk after having been on formulas for three or four days, either did not contract the disease, or if they did, survived their illness. Two babies who were discharged three or four days, respectively, before the ward was closed subsequently developed the disease. From the above facts it is evident that the formula-fed babies died while the breast-fed ones survived, although all babies received some formula.

Formula-Fed Babies

Died	18	Ages, 3-28 days
Lived	7	Ages, 1-3 days

Breast-Fed Babies

Died	None	
Lived	6	Ages, 7-14 days

Formula- But Subsequently Breast-Fed Babies

Died	None	
Lived	8	Ages, 5-11 days

PATHOLOGY

Autopsies were performed upon 16 of the 18 babies that died in Milwaukee Hospital. One-half, or 50 per cent, of these infants were premature. Marked dehydration and emaciation was the most conspicuous finding in 14, or 87 per cent. Acute enteritis was the most common lesion in 87 per cent, and pneumonia was next most frequently found, although it predominated over all other findings in only three of the babies examined. Often the pneumonia was the result of aspiration of food. In two of these, pneumonia was undoubtedly the cause of death for there was no evidence of enteritis.

PHYSIOLOGY

Diarrhea is a common disorder and is manifested in a great number of diseases, some of which are not primarily gastroenteric. Increased peristalsis and increased frequency of evacuation of the intestines occur in most febrile diseases, especially respiratory infections, in toxic or altered metabolic states, such as uremia and acidosis, exposure to high or low external temperatures, and in certain types of allergy. Diarrhea in early infancy is of special significance, because the younger the child the greater are the consequences of the loss of water and electrolytes.

Loss of weight is largely due to dehydration of the body. Water and salts are lost in large quantities from the interstitial spaces, and the plasma volume is reduced. The most important cause of the production of acidosis is undoubtedly severe loss of base in the stools. If there is inadequate renal function, sufficient acid is not secreted by the kidneys and compensation is not provided.

Clauson has shown that in conditions of dehydration lactic acid in the blood may be greatly increased.

In diarrhea much of the carbohydrate undergoes fermentation with the production of the lower volatile fatty acids. Acids with less than twenty carbon atoms can be recovered from the stools in increased amounts. These were formerly called irritants and thought of as an etiologic factor, but recently this has been shown to be doubtful. Altered chemical conditions, especially in the duodenum, which normally is sterile, permit abnormal amounts of bacterial growth. It is suggested by Plantenga and Jordan that these organisms elaborate toxic products. The absorption of foodstuffs is inadequate due to rapid peristalsis, and possibly, also, to an inability of the intestinal epithelium to absorb them.

Protein metabolism is very little affected, but fats and carbohydrates are considerably so. Much of the fat intake is found in the stool, mainly in the form of mineral fat. Carbohydrates are absorbed poorly, and the residuum is fermented, and the products of fermentation can be recovered from the stool.

Besides loss of water in the stools, a loss of minerals is also important, especially sodium, potassium, and chlorine. Acidosis results if elimination by other organs of the body is insufficient.

BACTERIOLOGY

Bacteriologic procedures have failed to discover a common etiologic agent. It seems apparent that the bacteriologic studies of infectious diarrhea in the newborn present a special problem. It is evident that infants are nonresistant to organisms which are of little or no virulence to the adult. It is probable that infection in the newborn infant often has its origin in adults with mild diarrhea. The hemolytic streptococcus was certainly the most common one isolated. From the stools it was cultured in all 16 cases studied. Blood cultures showed it twice, and, in throat cultures taken on 14 affected babies, it appeared in 100 per cent of the cases.

Post-mortem bacteriology also showed a prevalence of hemolytic streptococcal infections. Cultures of peritoneal fluid made on 13 babies showed this organism in 10 or 77 per cent, negative in 2 or 8 per cent and a mixed infection in the remaining one. Blood cultures revealed hemolytic streptococci in 2, or 14 per cent, gram-negative bacilli in 2, or 14 per cent, and pneumococci in 1, or 7 per cent. One lung culture showed hemolytic streptococci. Blood cultures were negative in 9, or 64 per cent.

SYMPTOMATOLOGY AND FINDINGS

At times the condition was preceded for one or two days by prodromal symptoms such as occasional vomiting, arrested weight gain, listlessness, and refusal at feedings. More often, however, the onset was acute and the clinical picture rapid in its course. A healthy robust baby within twenty-four hours would appear shocked and prostrated. The incubation period varied from forty-eight to ninety-six hours.

Diarrhea was usually the symptom presented in the beginning. The stools were increased in frequency to four and five daily. Consistency was good except that now and then a loose stool was passed. Soon, however, the frequency of the stools increased and finally they became only loose and watery. Usually, the stools were yellow, and occasionally greenish in color. The stools contained no curds or blood but occasionally mucus. Some of our babies were passing as many as seventeen stools a day.

Loss of weight was second in appearance. Even babies who had only a mild attack of diarrhea lost considerable weight due to dehydration. The mucous membranes were dry, there was loss of skin turgor, the eyes were sunken, the facies wrinkled, the fontanels sunken, the abdomen retracted, and the color cyanotic and then ashen gray, and a mental torpor with a feeble cry was present.

The temperature might be slightly elevated from 99° to 100° F. Occasionally, those with complications ran a fever as high as 103° or 104° F. Some of the babies even showed a subnormal temperature.

Distention was frequently present. Loss of appetite was a common symptom. Vomiting frequently occurred with regurgitation of food and subsequent aspiration of it into the bronchi, resulting in a pneumonia. A very few of the babies exhibited peristalsis.

TREATMENT

As far as treatment of the really sick baby was concerned, results were uniformly disappointing. In general, the infants did not respond satisfactorily to the recognized modes of therapy in diarrheal disorders. The usual measures of replenishing the dehydrated tissues, nourishing the patient, alkalinization, restoration and maintenance of mineral balance, and putting the bowel to rest were utilized.

A few of the special measures which were tried were the administration of a solution of 0.8 Gm. of sulfanilamide in 100 c.c. of normal saline subcutaneously in doses of 25 c.c. twice daily or 1 gr. of prontylin or 1 c.c. of neoprontosil given orally. These were rather heroic measures, and it is doubtful if they were of benefit to the infants. Transfusions of blood from donors who had taken 60 gr. of sulfanilamide in the twenty-four hours just prior to the giving of blood were also used. Convalescent serum was another agent used, but its efficacy could not be determined because numerous other agents were also being administered at the same time. The same was true of diplococcic filtrate and autogenous vaccine.

In the Milwaukee epidemic, breast milk was found to be an important adjunct in the treatment of infantile diarrhea. Not until the epidemic was well advanced was it possible to obtain a sufficient supply of mother's breast milk for these infants. Upon appeal to the Chicago Commissioner of Health, Dr. Bundeson, an ample supply was shipped to Milwaukee daily. Babies nursed upon human milk from the time of their birth were the only ones who either escaped or survived the epidemic.

Control measures employed prior to the outbreak of the epidemic were the usual ones laid down for the care of the infant from birth to its entrance into the nursery and thereafter. The basic principle involved was that everything coming in contact with the baby's mouth or nose should be in a surgically aseptic condition.

In all probability the simplest solution of this problem is the dispersion of the nursery. Spivek suggests an increasing degree of dispersion and safety by using: (1) cubicle units each completely equipped; (2) nurseries of no more than three or four beds to be closely associated with a similar number of maternal beds; (3) newborn infants housed in rooms adjacent to or in the mother's room; (4) hospital delivery and discharge within forty-eight hours, and (5) the ultimate of dispersion, frank home delivery.

Since the epidemic of 1938, the nursery at Milwaukee Hospital is being maintained under very strict precautionary measures. Overcrowding has been avoided and the nursery has been broken up into three divisions. Two are located on the third floor and will be designated as nurseries "A" and "B," and a third is on the fourth floor which accommodates any overflow and will be called nursery "C." Both nurseries on the third floor have been equipped with air-conditioned cubicles. Nursery "A" accommodates 18 cubicles while nursery "B" which is completely air conditioned in itself contains 12 similar air-conditioned cubicles. There are no cubicles in the fourth floor nursery but there is available 4,446 cubic feet of space for 12 cribs. An isolation room is maintained in another section of the hospital for the care of infected or suspected babies.

The cubicles can best be described by studying the illustration (Fig. 1). It is noted that air is sucked in through a filter in the top, and that the baby is completely isolated by glass partitions and front window. All clothing is stored in cabinet below. The babies are fed their formula, bathed, and diapered by the nurse without being removed from the cubicle or crib. The danger of contamination from the dressing or diapering table is thereby avoided. Each baby is carried individually and not in a conveyer to its mother. Special nurses and of course visitors do not enter the nursery. Attending physicians and nurses wear

caps, masks and gowns in the nursery. Nurses having skin infections and colds are excluded from the nursery. Throat cultures should be done on all nurses before they begin nursery service. The importance of hand washing is stressed especially between babies, before feedings, and after changing diapers.

All formula is prepared, bottled, capped, and labeled in a laboratory adjacent to nurseries "A" and "B" by a graduate nurse who has no other duties. Of course all equipment and bottles are autoclaved.

Fig. 1.

Children are not permitted on the maternity floor. Visiting should be discouraged, and during nursing hours is forbidden. Sitting and laying of outer garments on beds by visitors is discouraged.

All infants' records are kept at a desk outside of the nurseries. With this arrangement and the necessity of the attending physician donning cap, mask, and gown before entering the nursery, traffic in and out is reduced to a minimum.

The efficiency with which air conditioning and isolation by means of cubicles has reduced the possibility of air-borne infections is amply illustrated by the results of exposing culture plates. Open Petri dishes containing media for the

growth of hemolytic and nonhemolytic streptococci were left for a fixed period of time in occupied and unoccupied cubicles and in all of the nurseries. They were then incubated and the colonies counted. The most striking finding was the comparatively high count found in nursery "A." There nursing activity is the greatest and the air unfiltered. Three to ten times as many organisms were present in comparison to findings in a smaller air-conditioned nursery "B" directly across the corridor. The cubicles, however, in both nurseries showed similar minimal bacterial growths, demonstrating that the filter of the cubicle can reduce the air-borne infections satisfactorily. It was found that unoccupied, recently cleaned cubicles and cubicles with recently changed filters had the lowest number of organisms. In nursery "C," where crib space is the maximum and activity the minimum, bacterial counts were no higher than those found in the cubicles. Nonhemolytic streptococci were found about ten times as often as were the hemolytic type.

SUMMARY

1. Epidemic infectious diarrhea is a definite entity.

2. The disease is extremely contagious. More than one-half of the infants exposed to the infection contracted the disease.

3. Acute enteritis and pneumonia were the most common pathologic findings.

4. Bacteriologic studies showed that the most common invading organism was the hemolytic streptococcus. The average incubation period for development of symptoms varied from forty-eight to ninety-six hours.

5. The severity of the infection was illustrated by the rapid progress of the disease and its concomitant very high mortality rate, namely, 82 per cent.

6. Only formula-fed babies died. Breast-fed infants either did not contract the disease or if they did were able to conquer the infection.

7. Treatment was unavailing except for the feeding of mother's milk.

8. The small nursery with air-conditioning unit permits the growth of the minimum number of air-borne bacteria. Air-conditioned cubicles in large nurseries accomplish the same thing but cubicles add the important factor of isolation to the protection of the baby. Many small air-conditioned units containing individual cubicles with a completely isolated formula kitchen are the ideal set-up for the modern hospital nursery.

CONCLUSIONS

Tremendous immunity and therapeusis are conferred to a nursling by the feeding of mother's milk. Since the epidemic, a strenuous effort has been made to increase the incidence of breast feeding.

Grateful acknowledgement is made to Dr. C. J. Allen for material used in this paper.

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THE EFFECT OF THYROID ON STERILITY IN NORMAL AND HYPOTHYROID FEMALES

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INTERRELATIONSHIP between the thyroid gland and gonadal function has long been suspected (Marine[1] and Achneur[2]), and a large amount of data correlating sterility with cretinism and myxedema, in both males and females, has been accumulated. Moreover, milder conditions of hypofunction of the thyroid gland are thought also to be a factor especially where no other demonstrable pathology exists. This latter fact was first suggested by Litzenberg[3] who demonstrated that 45 per cent of those having a low basal metabolic rate were sterile. Likewise, Rowe[4] also showed that abnormal thyroid function is associated with sterility in over 30 per cent of a series of 2,549 cases. Although Berkman[5] and Hutchens[6] warn that a low basal figure is not always indicative of thyroid dysfunction (but should be considered as an indication of some metabolic or endocrine disorder), many[7] have recommended that thyroid extract be given routinely, even to those with a normal basal metabolism, feeling that this is a valuable adjuvant because of its stimulating properties.

The present investigation was undertaken, to determine the efficacy of giving desiccated thyroid to a group of sterile women, whether or not demonstrable thyroid hypofunction was present.

MATERIAL

All patients, with few exceptions, were from the service of an active gynecologic clinic. They represent a fair cross section of the reproductive span of the average female, the youngest being 21 years, the oldest 40 years of age. The average for the studied group of cases was 29.9 years at the time treatment was started.

In all, 71 cases with a normal or lowered basal metabolism were investigated, of which only 16 were selected for the present study. The latter were chosen because, as far as could be determined, they were entirely free from all pathologic processes, the correction of which might possibly have been effective in relieving the sterility. Thus, for example, one case, presenting clinical evidences of hypothyroidism, was excluded, because of a second degree retroversion and an endocervicitis.

It was felt, therefore, that the 16 selected cases might demonstrate the efficacy of thyroid therapy, since all other known factors which might be instrumental in producing sterility were eliminated.

No patient was considered as sterile until at least one full year had elapsed after marriage, during which time, notwithstanding normally frequent sex relations and the absence of contraceptive devices, pregnancy had not occurred.

METHODS

After taking a complete history, a thorough physical examination was made, at which time all endocrine stigmas were carefully noted. Laboratory analyses consisted of complete blood counts and chemistry; routine smears for the gonococcus, and hanging drops for the *Trichomonas vaginalis;* urinalysis; Wassermann; and determination of the basal metabolic rate. In those instances where repetition of the basal rate was deemed necessary, the lower, or lowest figure was considered as most correct.

Wherever possible, either a fresh or a condom specimen of the husband's seminal fluid was examined. Spermatozoa counts, number of abnormal forms, compatability with the endocervical mucus of the wife (Kurzrock[8]) and duration of viability were recorded.

Since occlusion, spasm, or stricture of the Fallopian tubes is one of the largest single mechanical factors causing sterility, the presence of this pathology would have to be eliminated. Therefore, in most cases, tubal insufflation was performed according to the technique of Rubin.[9]

Desiccated thyroid (U.S.P.-X) was given each patient, starting with 1 gr. per day and increasing the dose 0.5 to 1 gr. per day at semiweekly intervals, until a maintenance tolerance was reached. Constant checks for changes in blood pressure and pulse rate, for the appearance of fine muscular tremors, and for the presence of urinary sugar and albumin, especially where a normal metabolism was present, were made at frequent intervals. The basal rate was often rechecked after thyroid had been given for four to five weeks, and by adjusting the dosage, the rate was kept between a +10 per cent and a +20 per cent; i.e., at or just above the upper normal limits. If weight loss was desired, a low caloric diet was given, but no patient was advised to lose more than 2 to 2.5 pounds per week.

Thyroid was continued indefinitely at optimal dosage, and as soon as pregnancy was definitely established, the amount was readjusted. This readjustment was a reduction in amount, as pregnancy progressed, from one-third to one-half the maximal prenatal dose, since Baer[10] and Cornell[11] have shown that the basal rate increases from 25 to 35 per cent above the normal as term is approached. Medication also was continued during pregnancy, as prophylaxis against abortion,[3, 12, 13] and because it was felt that the strain, even with a mild thyroid deficiency, might lead to toxemia.[14-16]

RESULTS

Since the 16 cases, selected from the entire series, were free of pathology, they may be taken as a criterion of the efficacy of thyroid therapy in relieving sterility. These cases, accordingly, were classified into two separate categories, 9 patients who successfully conceived (Group A) and 7 who remained sterile (Group B). A complete summary of the findings for these two groups is presented in Tables I and II.

Examination of these tables reveals certain facts, which require further elucidation:

Menses.—Menstrual disorders were common, but more so in Group A, where 77 per cent suffered from abnormalities of the flow itself. In 7 cases clots were noticed. Menorrhagia was present in 3 cases, dysmenorrhea in 4, and oligomenorrhea in 1. One patient (6-A) who had been sterile for fifteen years, and who was under treatment solely for obesity and mild menopausal complaints, stated that, although her cycle was perfectly normal, the amount of flow had decreased considerably during the twelve months preceding treatment. In Group B, 71 per cent had menstrual disturbances, 2 complaining of menorrhagia, 3 of dysmenorrhea, and 1 of oligomenorrhea.

Irregularity in the cycle itself was far more marked in the A group (55 per cent). Since periods varied from nineteen to forty-six days, no definite rhythm could be established in 4 cases (2-A, 3-A, 4-A, and 5-A). In Group B this particular abnormality was encountered less frequently (14 per cent), only one

TABLE I. GROUP A* (BECAME PREGNANT)

Case	1	2	3	4	5	6	7	8	9
Age (years)	28	27	26	29	29	40	21	32	29
Married	6 yr.	5 yr.	5 yr.	3 yr.	---	15 plus yr.	19 mo.	---	4½ yr.
Duration of sterility	5 yr.	6 yr.	18 plus mo.	2 plus yr.	14 mo.	15 yr.	19 mo.	6 yr.	1½ yr.
Catamenia	14/21-31/4 Dysmenorrhagia	12/28-36/5 plus Menorrhagia	12/25-35/2½	14/19-46/2 Dysmenorrhagia, oligomenorrhagia	13/28-36/5 Dysmenorrhagia, menorrhagia	15/28/2-3 Menopause	13/28/4 Menorrhagia	13/21-28/6 Menorrhagia	14/31/5 Dysmenorrhagia
Premenstrual tension	++ backache	+ headache (1 day) backache	+++ backache (1 day)	++ nervousness backache headache (3-4 days)	0	0	++ (1 day)	++ headache (1-2 days)	+++ (2 days)
Libido	Mild	None	None	Mild	Normal	None	None	Mild	Mild
Weight (pounds)	178	212	144	152	138	176	130	186	140
Height (inches)	60	60	60	62	60	62	63	59	61
Insufflation	(1) normal	(1) normal	(1) normal	(1) mild spasticity	(1) normal	---	---	---	Normal

Endocrine stigmas	Dryness of skin, scalp and hair; hair on face; pelvic hair abnormal	Brittle nails; dryness of skin and scalp; thick coarse skin; hair on face; pelvic hair very thick; enlarged thyroid; pitting edema (subclinical myxedema)	Hair on face; dryness of skin and scalp; slight exophthalmos	None	None	Dryness of hair and skin; facial hair; pelvic hair abnormal	Mild pitting edema	Dryness of hair; abnormal pelvic hair of male type; facial hair; brittle nails	Dryness of skin, scalp and hair; facial hair; enlargement of thyroid
Basal metabolic rate	-10%; -12%	-28%; -28%	-26%	-10%	-16%; -18%	-14%	-10%	-18%	-12%
Cholesterol (mg./c.c.)	178	385	400	---	---	220	155	---	200
Thyroid (gr.)	iii	xii-xxiv†	iv	iii	iii	iv	iss	iv	iii
Duration sterility after thyroid (months)	12	13 (2)†	4	7	5	3	4	6	6
Pregnancy	Normal	Hypertensive toxemia	Normal—secondary inertia in labor; postpartum hemorrhage	3 weeks premature	Normal	Induced abortion	Spontaneous abortion due to accident	Normal	Normal, premature 1 month

*In all cases blood counts, urinalyses, Wassermann reactions and semen analyses were normal.

†This patient took 12 gr. of thyroid per day for 11+ months; through error dosage was doubled (24 gr. per day) for 2+ months.

TABLE II. GROUP B* (REMAINED STERILE)

Case	1	2	3	4	5	6	7
Age (years)	29	36	24	29	38	37	24
Married (years)	7	6 plus	2½	4	16	16	2½
Duration sterility	5 yr.	6 yr.	20 mo.	3 yr.	7 yr.	15 plus yr.	2 plus yr.
Catamenia	16/29-33/4 Dysmenorrhagia	14/28/5	11/28/4-6 Dysmenorrhagia	12/31-39/2 Mild oligomenorrhagia	13½/21/5	15/24-29/5 Dysmenorrhagia	13/28-30/5-6 Menorrhagia
Premenstrual tension	++ (1 day)	+ (1 day)	++++ (4 days)	0	+ (1 day)	+++ (2 days)	+ (mild)
Libido	Subnormal	None	Normal	Sl. subnormal	None	Slight	None
Weight (pounds)	141	140	118	130	158	166	144
Height (inches)	64	62½	62	62	61½	63	62½
Insufflation	(2) Normal	(1) Normal	(1) Normal	(1) Normal	(1) Normal slight opacity	Normal	Normal
Endocrine stigmas	Hair on face; pelvic hair showed male type	Dryness of skin, scalp; brittle nails; enlarged thyroid	None	None	Dryness of hair; facial hair marked	Hair on face; acne; enlarged thyroid	None
Basal metabolic rate	+14%; +7%	+8%; +12%	+10%; +12%	+11%; +3%	+10%; +10%	+4%; +8%	+9%; +11%
Cholesterol (mg./c.c.)	200	175	---	175	---	175	---
Thyroid (gr.)	ii-iii	i-iii	iv-v	ii-iii	iii-iv	iii	i-iii
Duration treatment (years)	2½	1½	1	1½	1 plus	2	1 plus

*In all cases, blood counts, urinalyses, Wassermann reactions and semen analyses were normal.

case presenting any marked deviation. These findings agree essentially with those of Lawrence and Rowe,[17] who have demonstrated that menstrual disturbances, independent of pelvic disease, were common in this type of patient.

Premenstrual tension, in different degrees of intensity and duration, occurred frequently. The symptoms causing the greatest number of complaints, in order of severity and frequency, were: Lower back pain, nervousness, irritability and headache, starting from one to four days before the onset, during the period itself, or in one instance, postmenstrually. This was most marked in Case 3-B, where excitability, depression, and exhausting nervousness, three to four days premenstrually, necessitated confinement to bed for that period.

As the result of the administration of thyroid, the intermenstrual intervals tended to approach an average, especially in those cases where a lowered basal metabolism was found. However, no change in the character of the menses themselves occurred, except for a mild relief of dysmenorrhea in 2 cases (4-A, 4-B). Premenstrual tension was increased in 7 cases, relieved in 5, and unchanged in the remaining 4. No correlating factor could be found to explain these results.

Libido.—Although the number of sexual congresses was considered normal, the degree of libido was low. In Group A, 44 per cent were completely frigid; 44 per cent had a mild degree of sexual satisfaction, and only 12 per cent were normal. In Group B, 28 per cent were frigid, 52 per cent subnormal, and the remainder normal. Slight increases were noted after the administration of thyroid, in both groups, but not sufficient to find agreement with Murray,[18] who believes that the effect of thyroid in sterility is due, in part, to increased libido occurring after its administration.

Obesity.—Obesity, per se, may act as a mechanical deterrent to fertilization, due, either to improper copulation or improper dissemination of the ejaculate in the vaginal vault. In comparing with the average height-age-weight tables, a marked tendency toward obesity is noted, Group A being 34 per cent overweight (average weight 163 pounds, statistical average 121 pounds) and Group B, 12 per cent overweight (average weight 142 pounds, statistical average 126 pounds).

Weight loss with thyroid, and where necessary a low caloric diet, was gradual. The maximum in any one week was 8 pounds (2-A) and the average from 2 to 2½ pounds. Weight loss was proportionally greater in those women who were markedly obese, despite the fact that all were taking tolerance doses of thyroid. With only one exception (2-A) the average weight at which conception occurred in Group A was 132 pounds. In those cases which remained sterile (Group B) the minimal weight during the period of study was also 132 pounds. It is interesting to note that the one exception (2-A) was 173 pounds when she conceived. These findings would militate against the factor of obesity as a deterrent to conception.

Endocrine Status.—Endocrine stigmas, other than obesity and menstrual disturbances, were far more common in the A than in the B Group. In the A Group, abnormal dryness of the skin, scalp, and hair were present in 5 cases; abnormal hair distribution on the face, cheeks, upper lip, and chin in 7 cases; extreme brittleness of the nails in 7 cases; and enlargement of the thyroid in 2 cases.

In the B Group, abnormal dryness of the skin and appendages, and abnormal hair distribution occurred in 3 cases and enlargement of the thyroid in 2 cases.

Subjectively, over 75 per cent of Group A patients complained of variable degrees of lethargy, inability to concentrate, undue weariness and fatigue, weakness and inability to withstand the cold. While these complaints were also present in the second group, they existed in a much milder degree.

With the administration of thyroid, rapid and marked relief of all subjective symptoms occurred. This was especially noted in those cases where several subclinical signs of hypothyroidism were present. However, in these latter cases, changes in the skin, hair texture, and nails occurred more gradually. Hair distribution remained unaffected.

Basal Metabolic Rate, Cholesterol and Thyroid Status.—The normal range for the basal metabolic rate was considered as -10 per cent to +10 per cent; that for the fasting blood cholesterol from 150 to 200 mg./c.c. The average basal figure in

the group which became pregnant (A) was -17 per cent, and the fasting blood cholesterol 256 mg./c.c. The highest rate noted was -10 per cent and the lowest -28 per cent, the cholesterol varying from 155 mg./c.c. to 400 mg./c.c. In Group B, the average basal determination was +9 per cent with variations ranging between a +3 per cent and a +14 per cent. The fasting blood cholesterol averaged 183 mg./c.c., with variations between 175 mg./c.c. and 200 mg./c.c.

The fact that a normal basal was found was not accepted as reliable assurance that thyroid function was normal,[19] nor a low basal to indicate necessarily hypothyroidism (Litzenberg[3]). For a proper diagnosis, the basal was considered together with the cholesterol level, the physical findings and the subjective symptoms. Thus 5 cases in Group A (2, 3, 5, 6, and 8) must be considered as suffering from a mild degree of true clinical hypothyroidism, while the remaining 4 (1, 4, 7, and 9) present sufficient evidence to warrant a diagnosis of subclinical hypothyroidism. In Group B, only a diagnosis of normal thyroid function could be made, since all findings were well within the normal range.

Tubal Insufflation.—VanTongeren,[20] Rubin[9] and others have demonstrated that the mere dilatation of the cervical canal, the insertion of a sound into the uterus, or the passage of gas through ostensibly normal tubes is sufficient to relieve sterility. Therefore the number of patency tests was limited to a minimum. In the group which became pregnant, insufflation was done only one time in only 6 of the 9 cases. Of the remaining 3, one (6-A) was not treated for sterility, one (7-A) became pregnant before the test could be done, and the third refused on the ground that she had undergone the test about a year previously and had been ill for several weeks thereafter. The patients in Group B, likewise, were insufflated only once, with one exception (1-B) where the test was repeated at the end of the first year of treatment.

In neither group was any abnormality found. Little or no difficulty was experienced in the insertion of the cannula, and the passage of gas through the tubes was accomplished without excessive pressure. In all cases the peristaltic action of the tubes was normal.

Therefore, it was felt that tubal insufflation was not a factor in producing pregnancy, since both groups received approximately equal amounts of insufflation; since no abnormal findings were noted in the tests; and since 3 patients who were not insufflated conceived.

Duration of Sterility Following Thyroid Therapy.—Omitting one case (2-A), the average duration of sterility following thyroid therapy was six months. Case 2-A demonstrated the fact that a sufficient quantity of thyroid must be given. She had been taking 12 gr. of thyroid daily for eleven months without effect. Through an error, the dose was doubled without untoward results. After receiving 24 gr. daily for 2+ months, conception occurred.

In the second group (B) the longest any patient was under treatment was two and one-half years, with an average for the entire group of eighteen months.

Prenatal Course, Labor and Delivery.—Of the 9 conceptions, 7 carried to viability. Two aborted, one (5-A) after an automobile accident in the fifth month, and one (6-A) induced in the third month. Two (4-A) (9-A) delivered prematurely, three weeks and one month, respectively.

The patient in Case 2-A developed a true hypertensive toxemia in the seventh month, but was sufficiently controlled so that she was able to carry to term. Case 3-A attempted to abort in the third and fourth months, but was stopped by use of morphine and progesterone. This patient also had a prolonged labor, which was followed by a severe post-partum hemorrhage.

SUMMARY

Sixteen sterile women, free of all pathologic and infectious processes, were given desiccated thyroid extract in tolerance doses, regardless of the thyroid status of the individual. Nine of the entire group became pregnant; 7 remained sterile. In the 9 cases where pregnancy occurred, only 7 carried fetuses to viability, 2 aborting as the result of external trauma.

Five of those who became pregnant were suffering from true clinical hypothyroidism; the remaining four had unmistakable evidences of subclinical hypothyroidism. No evidence of thyroid dysfunction could be elicited in the group of patients who remained sterile.

Therefore, the effect of thyroid, as an adjuvant or curative measure for sterility, was only demonstrable where a definite lack of thyroid was present. Likewise, where no deficiency in thyroid metabolism existed, the addition of this drug was of no apparent value.

CONCLUSION

Thyroid has a definite and valuable place in the treatment of female sterility only if hypothyroidism is present. It is of little or no value where normal thyroid function exists.

CASE HISTORIES

The following 2 cases are presented in brief, because of their exceptional interest.

CASE 2-A.—Mrs. E. R., aged 27 years, was seen first in November, 1935. Complaint: sterility (6 years) and obesity since onset of puberty. *Past history:* Negative. Husband had gonorrhea ten years previously. *Catamenia:* 12/28-36+/5. Menorrhagia, mild dysmenorrhea. Some clots. No libido. Husband very active sexually.

Physical examination: Height 60 inches; weight 212 pounds; marked generalized obesity. Hirsutes of upper lip, chin, chest and extremities. Pelvic hair distribution resembled male type. Skin was thick, coarse, and dry. Mild pitting edema of face and legs. Thyroid slightly enlarged. Heart and lungs negative. Abdomen negative. Blood pressure 108/80; red blood count 4.1 million; white blood count 7,800; Wassermann negative. Complement fixation for gonorrhea negative.

Pelvic examination: Negative; slight mucoid discharge; smears negative for gonorrhea. Tubal insufflation (December, 1935) showed patency of tubes.

Basal metabolic rate: –28 per cent; *fasting blood cholesterol:* 385 mg./c.c.

Course: In eight months, on a low caloric diet and thyroid to 12 gr. per day, weight was reduced to 173 pounds. In October, 1936, through error, thyroid dosage was doubled without harmful effect. Last menstrual period Jan. 26, 1937. Friedman test positive Feb. 12, 1937.

Prenatal course: Thyroid was slowly decreased to 12 to 14 gr./day after the diagnosis of pregnancy. During the third month, after a particularly violent intercourse, patient began to bleed. Bleeding was controlled with bed rest and morphine. In the seventh month, the patient of her own volition discontinued medication. Two weeks later blood pressure rose to 180/100 mm. Hg. Urinary albumin was present and pitting edema of the extremities was noted. She complained of severe occipital headache, and was immediately hospitalized. Modified Stroganoff therapy plus 20 gr. of thyroid were advised, and ten days later her condition had returned to normal, except for small traces of albumin in the urine. Remainder of prenatal course was negative. Labor, delivery, and post-partum course were normal.

CASE 6-A.—Mrs. R. H., aged 40 years, had an original complaint (June, 1938) of obesity and mild menopausal symptoms. Married fifteen years. No pregnancies. No contraceptives. Libido absent for last five years. *Past history:* negative. Usual childhood diseases. Chronic cholecystitis since 1928.

Menstrual history: 15/28/2-3. Mild cramps. In last year bleeding had decreased both in amount and duration. Occasional hot flushes during the last three months.

Physical examination: Height 62 inches; weight 176 pounds. Moderate obesity of girdle type. Large pendulous breasts. Hair, skin, scalp dry; nails brittle. Some facial hair. Heart and lungs negative; blood pressure 135/80; pulse 66/min. Hg. 80 per cent; basal metabolic rate -14 per cent; fasting blood cholesterol 220 mg./c.c.

Pelvic examination: Vaginal mucous membranes pale. Cervix, uterus, and adnexa negative. Tubal insufflation not done.

Course: Thyroid gradually increased to 4 gr. per day. Basal metabolic rate +18 per cent. Weight loss averaged 2 pounds a week. Last menstrual period Sept. 10, 1938; Friedman test positive on Oct. 30, 1938. Because of advancing age she did not wish for a child, and so, against advice, underwent an induced abortion.

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A METHOD FOR RECORDING AND REPRODUCING FETAL HEART SOUNDS

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MANY statements concerning fetal heart sounds have been copied and recopied until they have actually become medical folklore. But since none of these are based upon accurate methods of measurement, we decided it might be worth while to see how much truth and how much fiction there is in these conclusions. Some of these are:

1. The fetal heart rhythm is the ticktack type, that is, systole and diastole are of the same duration.
2. The condition of the fetus can be judged by its heart rate. (Plass[1] does not agree with this.)
3. The first sound is always the accented one.
4. The maternal and fetal hearts vary directly in rate.

One of us (W. J. H.) examined and delivered the patients reported and the other (A. L. S.) did the graphic and auditory recordings of the maternal and fetal heart sounds.

REVIEW OF LITERATURE

The review of the literature reveals few successful attempts to record fetal heart sounds.

Strassman and Mussey[2-4] described a method of taking electrocardiograms of fetal hearts and the resulting small waves show in the maternal electrocardiogram.

These can be taken only late in pregnancy, up to seventy days before delivery. Seventy records on 52 patients were taken and the fetal waves showed in 87 per cent. They state, "The faster the pulse of the mother, the faster is that of the fetus and vice versa." Lian, Golblin and Minot[5] examined fetal hearts by graphic methods (the number is not stated) and found the duration of the systoles to be 0.16 second and the diastoles from 0.16 to 0.19 second. The first sounds were 0.06 and the second 0.05 second in length while the second was greater in amplitude. Usually the sounds, due to reduplication of the first, were in three parts when heard through the loud speaker. They also state, "We have been able, further, to cut a few records." Pommerenke and Bishop[6] report they have made a few disc records of fetal heart sounds and have continuously made audible the fetal heart sounds in the delivery room. Mathews[7] has developed an apparatus for broadcasting fetal heart sounds during delivery but makes no statement as to permanent records. DeCosta[8] has developed what he calls a photostethoscope which changes sound into flickers of light, thus the fetal heart sounds are followed by observing the light flickers. Orias and Braun-Menendez[9] state the recording of fetal heart sounds is very difficult and this explains why so few of such studies have been made. They have included 2 fetal heart sound tracings made by Periera which are very good. They mention the graphs of Hofbauer and Weiss[10] (1908) and Beruti[11] (1923) but say these are not clear enough to distinguish the vibrations.

METHODS USED IN PRESENT STUDY

By means of the stethograph, the fetal heart sounds were photographed on a moving film simultaneously with the mother's electrocardiogram (Leads I and II) and pulse, thus showing the rates and rhythms of each and the rate relation between the fetal and maternal hearts. With the third lead, the mother's heart sounds were stethographed. These records admit of accurate measurement of fetal heart rates, of duration of the sounds, of duration of systole and diastole and observation of the fetal rhythm. By measuring the deflections in the electrocardiogram, the exact rate of the mother's heart is known.

After the above recordings, the fetal and maternal heart sounds were recorded on the same disc. This admits of careful study (at slow or normal speed) of these sounds, of murmurs and any change in rhythm. Since heart sounds of different persons have their own peculiar quality characteristics (somewhat as voices do), these can be preserved and can be reproduced with all the tone peculiarities.

After recording, the heart sounds were studied when audited through the loud speaker and many variations were heard that were not recorded in the stethograms or the discs.

THE STETHOGRAPH

The stethograms of the fetal heart sounds were taken by means of the stethograph developed and reported by Bierring, Bone, and Lockhart[12] in 1935. Technical and constructional details of this instrument are given in their article.

The stethograms of all fetal heart tones shown are recorded at the rate of 25 mm. per second so longer strips may be viewed and the many variations of the sounds can thus be seen.

DESCRIPTION OF THE CARDIOPHONOGRAPH

The cardiophonograph, developed by one of us (A. L. S.), is employed to amplify the heart sounds so they may be heard through a stethophone or a loud speaker and then recorded on special phonographic discs. All mothers' heart sounds were recorded on the same disc with the fetal heart sounds, each occupying about one-half the record.

At times the sounds are hardly discernible in the stethogram and are hardly audible in the disc recordings. In three cases the fetal heart sounds could not be heard through the acoustic stethoscope but were successfully recorded and reproduced.

This instrument is built into a compact carrying case and the loud speaker of the electrodynamic type is located in the detachable cover.

The microphone is of the crystal type and separated from the abdominal wall by a bell of soft rubber which "seals" itself to the tissue located over the most favorable fetal heart tone area. After the sounds are changed into electrical impulses, they are conducted through a four stage vacuum tube amplifier, with a gain of 120 decibels, to the cutting head which is of a permanent magnetic type. The pickup is of the crystal type. The input impedance matches the crystal microphone.

The recording is at a rate of 78 revolutions per minute and the discs are composed of a substance with an acetate base on an aluminum plate and can be audited many times without injury. Comments are recorded on the record.

A loud speaker or stethophones are used to assist in selecting the area in which the heart tones are most suitable for recording.

For reproduction, which can take place as soon as the recording is finished, a three-stage amplifier with a gain of 70 decibels is placed between the pickup and the loud speaker. The frequency response ranges from 50 to 8,000 cycles per second. The low or high frequencies can be selected at the will of the operator. The records can be reproduced on any phonograph.

NUMBER OF PATIENTS AND AGE OF FETUSES

On 58 pregnant mothers stethograms and disc recordings of the fetal heart sounds were made. In 52 of these cases the results were successful and both stethograms and cardiophonograms were completed and preserved. But with experience acquired in the first 36 cases, we have been able to record the fetal heart sounds in each case since then, that is, the last 22 cases.

In the six cases in which recordings were unsuccessful, in one the fetus was five and one-half months and the other five were between seven and one-half and eight and one-half months. In all these, the heart sounds could not be heard by aid of the stethoscope, the electric stethoscope or the loud speaker. In each case the mother has since been delivered of a normal child whose heart is normal in every respect. As to the position of the fetuses (no twins), 56 were vertex presentations and two were breech.

In five cases the attempt to record the fetal hearts resulted in failure but at later periods the recordings were entirely successful.

In the successful recordings the period of pregnancy varied from five months to three days before delivery. Three disc recordings were made during delivery and several other fetal heart sounds were broadcast before and during delivery but are not included in this series.

PATTERN OF FETAL HEART SOUNDS

The fetal heart sounds are definitely not of the ticktack type, but are as individual as those developed in the adult organ. Either sound may be accentuated but, contrary to past teachings, the second sound in a majority of cases is of greater intensity. In 28 cases the second sound is definitely of greater intensity (louder) than the first; in 8 cases the first sound is accentuated and in 16 cases the two sounds, varying somewhat, are of about equal intensity. The first sound is usually of longer duration and consists of more vibrations (three to eight cycles) though of lower frequency. The first sound may be very wide at times, and this is due to the separation of the auricular sound from ventricular part of the first sound. It is fairly well established that the first sound is composed of an auricular element which follows the auricular systole,[13, 14] and the ventricular element which is either of valvular[15, 16] or of valvular and muscular[17, 18] origin. In Fig. 6 when the heart slows the auricular third sound (*a*) can be seen to appear before the principal vibrations of the first sound. This, of course, if still considered to be part of the first sound, would greatly increase its duration.

The frequency composition of fetal heart sounds is similar to that of adult heart tones. The sound energy is usually considerably less but at times the in-

tensity is, surprisingly, greater than the adult sounds (Fig. 6). However, the ear must operate close to the lower threshold of audibility and in extreme cases is incapable of detecting the sounds (9 in this series). Through the ordinary stethoscope, the acuity of hearing at low frequencies is obviously one essential requirement in obstetric auscultation, according to Williams and Dodge.[19]

FETAL RHYTHM AND RATE

The rhythm, as in the adult, is constantly changing but in all it seems to be of sinoauricular origin. The heart rate is variable and in some cases this is extreme, as in Fig. 6 it varies from 92 to 150. For the series of 52 the fetal heart rates range from 124 to 163. In two cases the first sound is reduplicated as shown in the stethogram (for example Fig. 7), but in the disc recordings, these give the impression of a presystolic gallop.

DURATION OF FETAL SYSTOLE AND DIASTOLE (VENTRICULAR)

The identification of diastole and systole is not as difficult as it seems, for diastole is nearly always the longer silence and the first sound is practically always wider than the second. By slowing the revolutions of the turntable when reproducing the recordings, the sounds and silences, due to the slow rate of reproduction, can be more easily analyzed.

It is difficult at times to know just where the systole begins, for as the auricular element of the first sound moves forward into the presystolic space it may separate from the first sound and become the presystolic third sound. If it is included in the duration of the systole, this greatly increases the duration of the systole graphically, even though the ventricular systolic contraction is really shorter.

The length of both systole and diastole is constantly changing though diastole is the more variable. As the heart rate decreases, both increase in duration, systole proportionately less than diastole. For example, in Fig. 6, when the fetal heart rate is 150 per minute, systole occupies 0.18 and diastole 0.23 second while, when the rate is 92, systole is 0.23 second in length and diastole is as great as 0.53 second (one complete cardiac cycle is 0.75 second and this is at a rate of 80 per minute).

In this series the systolic phase varies from 0.16 to 0.23 second, while the diastolic ranges from 0.17 to 0.53 second.

In one case (Fig. 3) diastole is shorter than systole; in two cases diastole and systole are equal, but in the rest of the series diastole is the longer of the two.

All measurements were made on stethograms which were exposed at a rate of 50 mm. per second, although in the illustrations the rates are always 25 mm. per second.

These measurements are not in agreement with those given by White[20] (number of heart rates measured and age not given), who states that in the human heart the duration of systole and diastole is approximately as follows:

At rate of 90 systole is 0.32 and diastole 0.34 second.
At rate of 100 systole is 0.30 and diastole 0.30 second.
At rate of 120 systole is 0.28 and diastole 0.22 second.
At rate of 150 systole is 0.23 and diastole 0.17 second.

In this series of 52 cases in only one fetus is the systole longer than diastole, and in this the heart rate is 163. All fetal heart rates, with two exceptions, are over 130 per minute, while one varies from 92 to 150.

Also these measurements do not agree with those given by Boone[21] who finds, in children at the rate of 126, systole (0.24) and diastole (0.24) are equal; between 126 and 180 systole is always of greater duration and below 126 diastole is always of greater length. However, it must be stated he starts the measurement of systole in line with about the middle of the ascending limb of the R-wave in the electrocardiogram which is taken simultaneously with the stethogram.

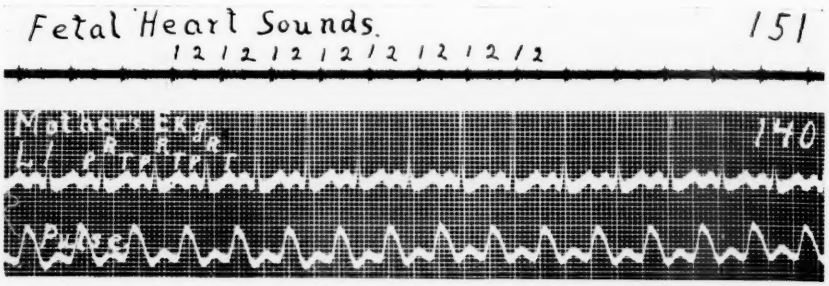

Fig. 1.—Rate 151. First sound (*1*) of greater intensity. Systole 0.17 to 0.18 second. Diastole 0.21 to 0.23 second. Vibrations first 5, second 4. Mother's heart rate 140.

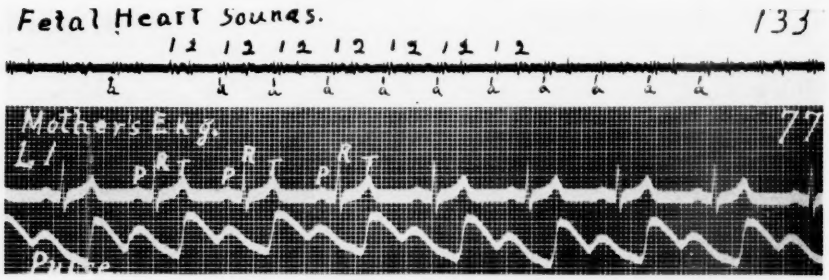

Fig. 2.—Rate 133. Heart sounds of about equal intensity. Vibrations low in frequency first (*1*) 1 to 3 and second (*2*) 3. Systole 0.16 to 0.17, diastole 0.27 to 0.29 second. Mother's rate 77. Presystolic third sound (*a*) is seen before every first sound but one.

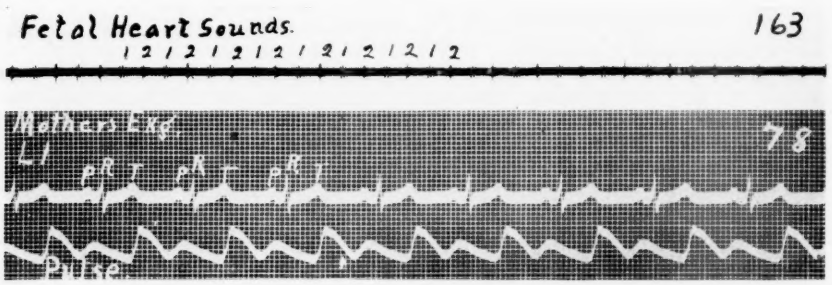

Fig. 3.—Rate 163. Second sound (*2*) of higher intensity and first (*1*) of lower frequency. Vibrations first 3 to 4 and second 1 to 3. Systole is of longer duration (0.18 to 0.19) than diastole (0.17 to 0.18 second).

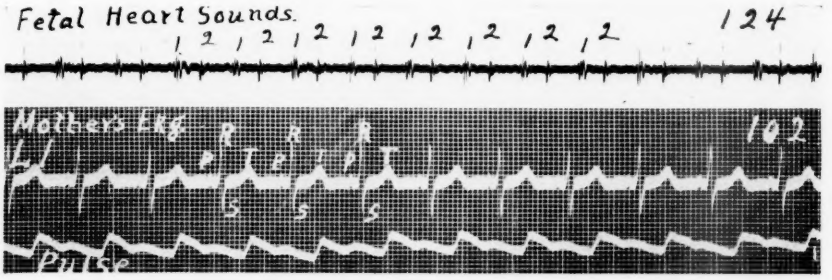

Fig. 4.—Rate 124. The second (*2*) is of much greater intensity and frequency. Vibrations first 3 to 5 and second 4 to 5. Systole 0.20 to 0.23 second. Diastole 0.25 to 0.27 second. Mother's rate 102.

In this series the systole is measured from the beginning of principal oscillations of the first sound, and when the auricular portion of the first sound appears in the presystolic area, it is not considered part of the ventricular systole.

As to the statement of Strassman and Mussey[2] that the rate of maternal and fetal hearts is in a ratio of 3:5 and 4:7, we must disagree, for the measurement of these heart rates taken simultaneously shows no rate relation between the two. For example, in one case the fetal heart rate is 163 and the mother's is 78, while in another, the fetal rate varies from 92 to 150 while the maternal rate remains at 82.

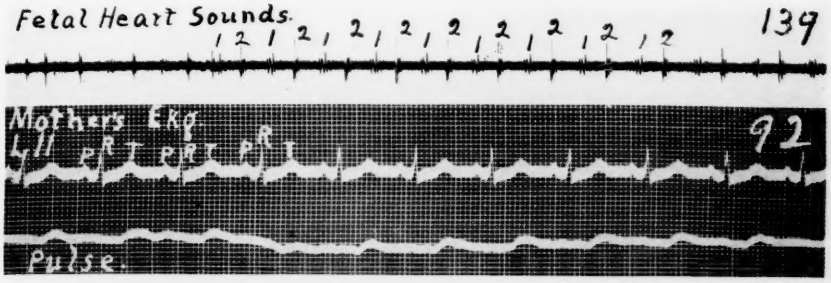

Fig. 5.—Rate 139. Intensity of the second (*2*) is very great (11 mm.) and the frequency is higher than that of the first (*1*). The amplitude is higher in the middle part. Vibrations of first 3 to 4 and second 4. Systole 0.20 to 0.22 second. Diastole 0.20 to 0.25 second. Mother's rate 92.

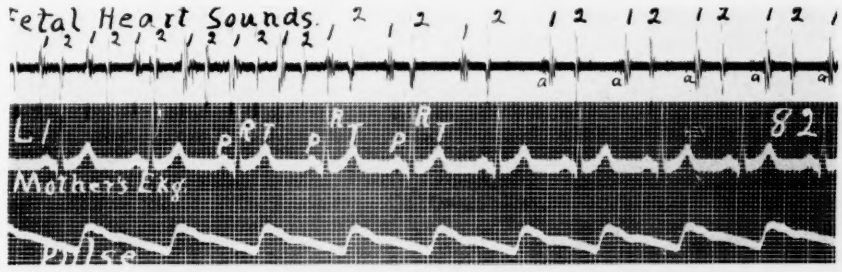

Fig. 6.—Rate 92-150. Amplitude of both sounds is very high, of the first (*1*) 21 mm. and second (*2*) 33.5 mm. As the rate decreases the auricular (*a*) part of the first sound advances into the presystolic area but the intensity of this sound is now lower. Vibrations first 4 to 8 and second sound 3 to 4. Systole 0.18 to 0.23 and diastole 0.23 to 0.53 second. Mother's rate 82.

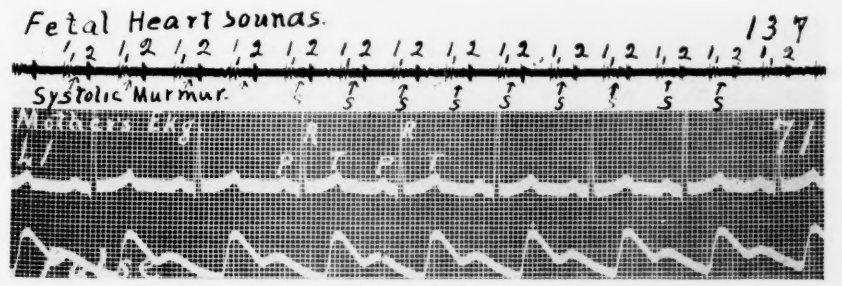

Fig. 7.—Rate 137. The second (2) is slightly greater in intensity than the first, which is split (1_1). The second part of the first sound is of low intensity and frequency, and this is followed immediately by a systolic murmur (*S*) of high frequency which continues into the second sound. Systole 0.17 to 0.19 and diastole, which is normal, 0.24 to 0.25 second in duration. Mother's heart rate 71.

AMPLITUDE OF FETAL HEART SOUNDS

The amplitude varies considerably in the stethograms, the first sound with a minimum of 3 mm. (Fig. 3) and a maximum of 22.8 mm. (Fig. 6), while the variation in the second sound is from only a slight oscillation in the base line at times (Fig. 1) to 33.5 mm. (Fig. 6). In the phonographic recordings the intensity of the sounds varies in just the same degree, in some they are loud and in others very soft but all discs considered successful recordings reproduce the heart sounds clearly enough so they can easily be identified. As a rule, hearing at low frequencies is difficult for the average ear, but in the reproduction of the recorded heart sounds these frequencies can be so amplified that the sounds are easily heard by the most inexpert. The intensity of the heart sounds varies greatly from time to time in the same patient.

RECORDING OF A FETAL HEART MURMUR

As far as we have been able to learn by a search of the medical literature, fetal heart murmurs have never been recorded in a stethogram or on phonographic discs. In this case, the mother, a primipara, when six years of age, had had her spleen removed "on account of some kind of anemia." She was in normal

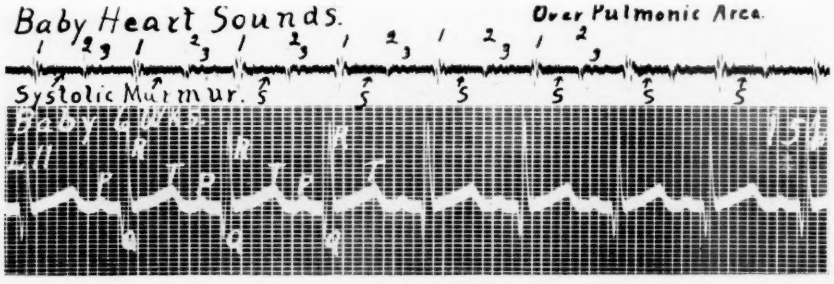

Fig. 8.—This record was taken six weeks after birth of the fetus taken in Fig. 7. Rate of exposure 50 mm. per second. The first sound (*1*) is of greater intensity and is biphasic, while the second (*2*) is directed upward. The third (*3*), which is proto-diastolic, is of low intensity and frequency. A systolic murmur (*S*) continues throughout systole. Systole 0.19 to 0.21 and diastole 0.1875 to 0.1975 second. Vibrations first heart sound 4 to 5 and second 2 to 3. Rate 151. The electrocardiogram is of the second lead and a deep Q-wave is present. The electrocardiogram and heart sounds are taken simultaneously.

physical condition at the time of this examination. The recordings were made on April 4, 1939, and the baby was born the nineteenth of the same month. The fetus was in an R.O.A. position, and this was confirmed by the roentgenogram.

The fetal heart tones were easily "picked up" and the recordings made without difficulty. The stethogram (Fig. 7) shows a definite split first sound (1_1) with a murmur in systole, starting just after the second division of the first sound and continuing to the second sound. The principal oscillations of the heart sounds are about equal in intensity and diastole is longer than systole. In the reproduction of the disc, recording the systolic murmur is clearly heard but varies in intensity with the mother's respirations and the movements of the fetus—the latter being definitely audible.

During the delivery, the fetal heart sounds were made audible through the loud speaker up to the time the baby's head appeared on the perineum.

Immediately after delivery the child was examined and a definite systolic murmur was heard over the upper sternum and the pulmonic area. The spleen was enlarged. No other abnormalities were found.

Six weeks after birth the child was again examined. It was undernourished, weighed 7½ pounds and the spleen was enlarged to 3 cm. below the costal margin and was rather firm.

The heart was about normal in size but the aorta was wider than normal. A systolic murmur, best heard over the upper sternum and the pulmonic area, was present and was transmitted about equally in all directions.

In the stethogram (Fig. 8), taken over the pulmonic area and part of the upper sternum, normal first and second sounds and a protodiastolic third sound are recorded, while a systolic murmur continuing throughout systole is seen. Systole is longer than diastole.

The electrocardiogram is normal except for a deep Q-wave in Leads II and III and a high T-wave in Leads I and II. In the disc recordings the systolic murmur, taken from over the pulmonic and upper sternal areas, is clearly audible, the rhythm is sinus in origin though variable, and the rate averages 150. No definite diagnosis was made at this time.

VALUE OF RECORDING AND REPRODUCING FETAL HEART SOUNDS

Many accurate, measurable observations are necessary to overcome misinformation concerning the normal fetal heart, and it is believed the methods described can be the principal means of doing this.

For teaching purposes a collection of records showing normal and abnormal fetal heart sounds can be made and reproduced so students can unquestionably see and hear what is being described.

Records can be taken during the course of pathologic cases, ablatio placentae, for example, and preserved to actually show the progression of the disease from the fetal heart standpoint.

The records will be of permanent value in studying the fetal heart response to drugs administered to the pregnant mother before and during confinement.

The records can be reproduced at leisure and the heart studied as many times as desired without alarming or tiring the patient.

Fetal heart sounds are an unsolved mystery as far as the average medical student is concerned, and some practitioners as well, but after he actually sees and hears the recorded sounds and hears those audited directly from the patient until he is familiar with their vagaries he is then prepared to auscultate the organ from which they emanate.

By broadcasting the heart sounds through the loud speaker, all in the delivery room can follow the normal changes in the fetal sounds, and to those of us who have done this, it is evident much time and study will be necessary before the normal and pathologic fetal heart changes can be differentiated.

When it is necessary to decide whether the child is alive or not this adds another method of examination and, with electrocardiography, it would be a rare case in which this question could not be accurately answered.

It is believed that, by this method, congenital heart lesions can usually be discovered before birth.

SUMMARY

In a series of 58 pregnant mothers, an attempt was made to make stethograms and reproducible disc recordings of the fetal heart. In 52 cases the effort was successful and in 6, unsuccessful.

The age of the fetuses whose heart sounds were recorded varied from five and one-half months to the time of delivery.

The fetal heart sounds were not of the ticktack type in 49 of the cases, the diastole being of greater duration than systole.

The length of ventricular systole ranged from 0.16 to 0.23 second and the diastolic phase from 0.17 to 0.53 second, and there was no constant change in the duration ratio between these periods at the various heart rates.

The heart rates varied from 92 to 163, and, since in all cases, except one with a congenital heart lesion, a healthy child was born, it seems rate changes in this range are of little diagnostic significance.

The first sound is seldom the accented one, this being true in only 8 cases. The intensity of the sounds was about equal in 16 cases and in 28 cases it was greater in the second.

The reported recording of a fetal heart murmur is thought to be the first described in the medical literature.

Congenital heart lesions may be recorded and diagnosed before birth.

A portable mechanism for recording and reproducing fetal heart sounds as well as making them audible directly from the patient is described and it is thought this will be of value (1) clinically, (2) in research, (3) in teaching, and (4) in increasing knowledge of changes, normal or pathologic, of rate and rhythm of the fetal heart sounds during delivery.

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1001 Federal Securities Building.

Herrnberger and Horstmann: Glycogen Content of Vaginal Epithelium in Children, Arch. f. Gynäk. **168:** 451, 1939.

The smallest amount of follicular hormone which will definitely cause a full and complete glycogen content in the vaginal mucosa in children and maintain it at this level was found to be a daily peroral dose of one thousand international units of estradiol benzoate. The authors' studies show that glycogen accumulation in the mucosa does not occur until after the epithelium has been stimulated by hormone therapy to the point where it has achieved its normal adult type of stratification. They believe that they have proved that the production of normal glycogen content is directly dependent upon ovarian function and that the follicular hormone is directly in control of glycogen formation.

Ralph A. Reis.

THE REDUCTION OF POST-PARTUM MORBIDITY BY THE PROPHYLACTIC USE OF ERGONOVINE*

JAMES B. LOUNSBURY, M.D., ANN ARBOR, MICH.

THE employment of an oxytocic immediately post partum has been practiced ubiquitously since John Stearns introduced the use of ergot in obstetrics in 1807. Few obstetricians, however, are convinced that the routine administration of such a drug over a period of several days is warranted.

Since the appearance of the article by Bourne and Burn[1] in 1927, a number of clinical experiments[2-6] have been made in an effort to demonstrate the prophylactic value of ergot and its derivatives. With the controversial[7-10] isolation of the active principle of ergot, now known under the pharmacopeial name of ergonovine,[11] an added interest in the subject was aroused. The time-honored fluid extract of ergot is now being abandoned to the more stable active principle.

The inconsistency in the results reported with the prophylactic use of the fluid extract of ergot has been enlightened by the work of Jones and Barlow[5] showing that the drug may undergo deterioration. Since the advent of ergonovine, studies on its effect on involution and puerperal morbidity have been invariably favorable.[12-16] The following study, undertaken at the Maternity Division of the University Hospitals in Cleveland, will add to the literature which has been accumulating since 1935.

PROCEDURE

Two hundred obstetric patients were studied (Table II), unselected except as follows: Patients with abdominal tumors, patients on whom observations were too inadequate to be of use, cesarean sections and very ill patients, such as cardiacs, were discarded for obvious reasons. Due to the nature of the University Hospitals' obstetric service, nearly all the cases were operative deliveries, the term operative including the so-called outlet or prophylactic forceps.

All patients received the routine administration of 1 c.c. of pituitrin (obstetric) following delivery of the fetus and 0.2 mg. of ergotrate (Lilly) following delivery of the placenta, both drugs given hypodermically. The first 100 cases, Series A, were given in addition 0.4 mg. of ergotrate orally six hours post partum and 0.2 mg. t.i.d. for the next three post-partum days. The second 100 cases, Series B, were given no oxytocic other than the routine pituitrin and ergotrate immediately post partum as noted above, unless alarming subinvolution, post-partum hemorrhage or foul lochia warranted further medication.

Daily measurement of the height of the fundus above the symphysis pubis, notation of the character and amount of lochia, and interrogation of the patients as to the presence and severity of afterpains were made by the same individual. Measurements were discarded when it was known or suspected that the urinary bladder was full. Uterine pains known to be associated with the process of nursing were not tabulated.

*The clinical work of this article was done while the author was a member of the resident staff of the Maternity Division, University Hospitals, Cleveland.

TABLE I. DATA ON LOCHIA

DAYS POST PARTUM	SERIES A (CASES GIVEN ERGOTRATE) PER CENT OF PATIENTS WITH					SERIES B (CONTROLS) PER CENT OF PATIENTS WITH				
	PROFUSE LOCHIA	MODERATE LOCHIA	SCANT LOCHIA	NO LOCHIA	LOCHIA ALBA	PROFUSE LOCHIA	MODERATE LOCHIA	SCANT LOCHIA	NO LOCHIA	LOCHIA ALBA
1	0	62	36	0	0	0	73	27	0	0
2	1	44	54	0	0	1	61	38	0	0
3	0	39	59	0	1	2	63	34	0	0
4	0	37	63	0	3	0	68	32	0	1
5	0	40	59	0	4	2	63	35	0	1
6	0	28	52	9	6	1	46	52	1	0
7	0	22	66	10	20	1	43	55	0	1
8	1	23	68	9	23	0	45	55	1	11
9	0	23	45	11	33	0	40	56	6	19
10	0	31	57	9	33	0	49	43	8	43

TABLE II

Series A (Patients given ergotrate):		
Primiparas	72	
Multiparas	28	
Total	100	
Primiparas having afterpains	40	(55%)
Multiparas having afterpains	25	(89%)
Total	65	(65%)
Series B (Controls):		
Primiparas	91	
Multiparas	9	
Total	100	
Primiparas having afterpains	39	(42%)
Multiparas having afterpains	8	(88%)
Total	47	(47%)

The standard of morbidity used was an elevation of temperature to 38° C. or over for two or more consecutive days. Temperature elevations due to causes other than uterine infection were not included in the morbidity statistics.

RESULTS

The determination of the rate of involution of the uterus was made by plotting graphically the mean average height of the fundi each day in each group of cases considered. Fig. 1 shows the rate and degree of involution of the 100 cases (Series A) receiving ergotrate during the first three post-partum days as compared to the same number of controls (Series B). Although the mean difference in the measurements amounts to about 0.5 cm. only, it is significant that the mean height of the fundi in Series A is at all times less than that of Series B. It is also significant that the rate of involution in Series A is a regular one throughout the period while that of Series B tends to slow down particularly in the last three days of the ten-day period.

Believing, as many have observed in their clinical experience, that multiparas involute less rapidly than primiparas, I compared the cases graphically in the group receiving ergotrate and the controls. Fig. 2 illustrates the comparative involution in multiparas and primiparas who received ergotrate. Surprisingly enough, the rate of involution in multiparas on ergotrate prophylaxis follows very closely that of primiparas. In Fig. 3, however, where the multiparas and primiparas of the control series are compared, it is seen that the involution of the multiparous uterus

is considerably more irregular and more delayed than the primiparous uterus with or without the administration of ergotrate.

In the use of prophylactic therapy with ergotrate, the effect on primiparas alone is shown in Fig. 4. Here again the actual difference in the mean height of the fundi does not amount to more than 0.5 cm., but it can be seen that there is a definite trend or tendency for the rate and degree of involution in the cases receiving ergotrate to be somewhat better than the controls. The same type of comparison is made in Fig. 5 with respect to the effect of ergotrate on the multiparous uterus, as compared to the rate of involution in the control. Here the benefit derived from oxytocic administration is much more marked, the measurements of the fundi averaging almost 1.5 cm. in difference.

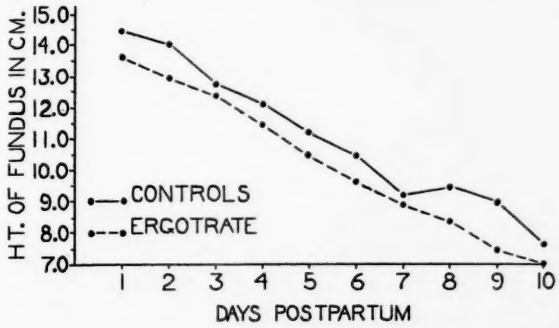

Fig. 1.—Graph showing the rate and degree of involution of the uterus of patients given ergotrate (broken line) during the first three post-partum days compared to the controls (solid line) who received only the routine oxytocics during delivery. The average height of the fundi in each group is plotted for each day of the post-partum period in the hospital. Notice the regularity of the line representing the uteri influenced by ergotrate and the irregularity of the controls; the latter show a tendency for the rate to decrease during the last three days.

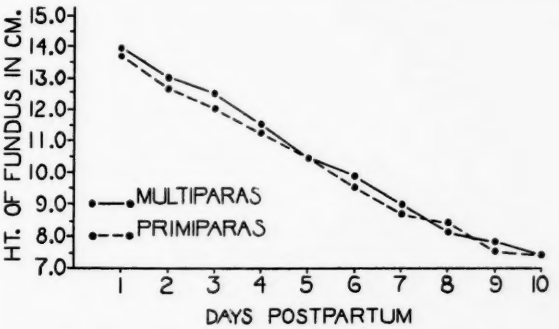

Fig. 2.—The curves, plotted in the same manner as in Fig. 1, show how closely the involution of the multiparous uterus (solid line) follows that of the primiparous uterus (broken line) when ergotrate is given during the first three days of the post-partum period.

A statistical study of the puerperal lochia can at best be rather inaccurate due to the inherent difficulty in determining the exact amount of lochia passed and due to the indefinite borderlines defining lochia rubra, lochia serosa, and lochia alba. In this study it is admittedly quite inaccurate in view of the fact that the description of the character and amount of lochia was based purely on personal judgment or impression. Since it may be assumed, however, that the same relative inaccuracy pertains to Series A as to Series B of the patients or, in other words, that the same percentage of error applies to the one group as to the other, some conclusion perhaps may be justified from a study of Table I. The cases are

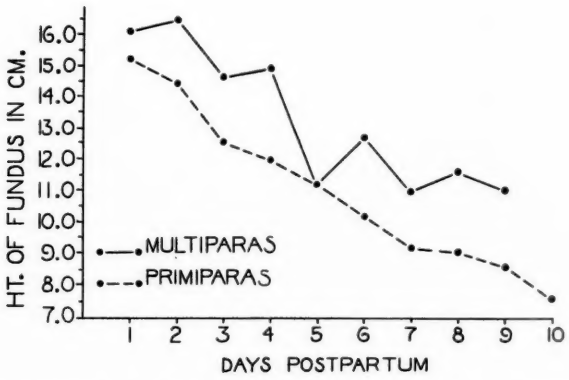

Fig. 3.—The involution of the multiparous uterus (solid line) compared to that of the primiparous uterus (broken line), neither of which groups was given the prophylactic course of ergotrate.

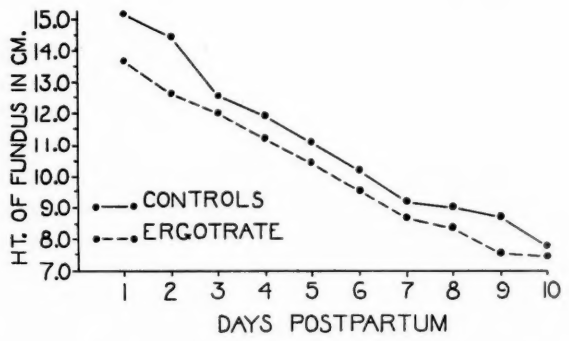

Fig. 4.—The rate and degree of involution of the uteri of the primiparas who were given ergotrate (broken line) and of those who were not (solid line). The mean difference of the two curves is about 0.5 cm.

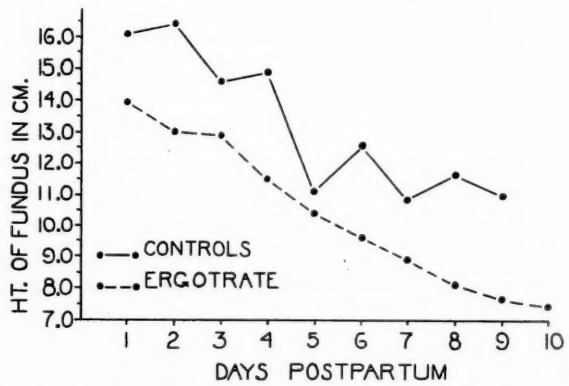

Fig. 5.—This graph illustrates the rate and degree of involution of the uteri of multiparas who received ergotrate (broken line) and those who followed the customary course without prophylactic medication (solid line). The mean difference of these two curves is 1.5 cm.

classified on each day of the ten-day post-partum period according to the amount of lochia passed. The greatest difference to be noticed in the two groups is in the incidence of lochia observed to be profuse and in the cases showing absence of lochia. Whereas only 2 per cent of those receiving ergotrate exhibited profuse lochial discharge, there was 7 per cent in the control group; and while the absence of lochia was found in 48 per cent of patients in Series A, it was observed in only 16 per cent of the controls. Likewise, Table I demonstrates the greater prevalence of the appearance of lochia alba in the group receiving ergotrate than in the controls.

A study of the incidence of "afterpains" in the primiparas and the multiparas of the two groups reveals some rather interesting facts (Table II). Of the 100 cases in Series A, 65 per cent had afterpains, while 47 per cent of the controls suffered afterpains. In Series A, 55 per cent of the primiparas had pains, while 42 per cent of those who received no ergotrate had afterpains. In the cases given ergotrate 89 per cent of the multiparas had afterpains, while 88 per cent of the multiparas in Series B had afterpains. It is seen, therefore, that the incidence of afterpains in the multiparas in the two groups was practically identical, while the incidence in the primiparas was only a little greater in those who were given ergotrate than in the controls. Incidentally, the occurrence of afterpains in primiparas does not seem to be so infrequent as is commonly believed.

The puerperal morbidity as determined by the standard mentioned above, that is, the morbidity due to uterine infection excluding all other causes, was found to be 4 per cent in the cases given ergotrate as compared to 10 per cent in the controls.

Side reactions of ergot therapy such as nausea and vomiting which occur with the fluid extract were not seen. There was no case of ergotism.

COMMENTS

The size of the dosage of ergotrate and its frequency of administration were chosen purely arbitrarily. It was felt that if 0.2 mg. of the drug would stimulate the tone and motility of the uterus, as shown by Davis and others,[7] for a period of at least two or three hours, little would be gained by subjecting the patient to the possible pain of more vigorous contractions. As shown in this series, the presence of afterpains was relatively little increased by the use of the drug in this dosage. Afterpains were readily controlled by codeine. It may be that the use of greater or more frequent doses of ergonovine would produce an even more marked exhibition of the value of the prophylactic administration of an oxytocic.

The impression was gained that the toxemias tended to involute much more rapidly than the normal cases. An attempt was made to compare the rates of involution of toxemias to normal cases in the group receiving ergotrate and in the control series by the same graphic method already presented. The group of cases of toxemias was too small, however, to be statistically utilizable and the results were too irregular to be of significance. The impression is maintained, none the less, that toxemias, especially eclamptics, tend to involute much more rapidly than normal puerperal cases.

The lack of accuracy obtainable in a study of this sort may make one discredit the results. It must be observed, however, that whatever inaccuracies in measurements and in observations occurred in the group of patients who were given ergotrate occurred to a like extent in the controls. More significant, however, in justifying the conclusions drawn is the fact that there is consistency in all the subdivisions of the study

in showing that the patients who were given ergotrate had a better and smoother post-partum course from the standpoint of clinical signs during the post-partum period.

The studies show that there is definitely a more regular rate of involution in the patients who received prophylactic doses of ergotrate than in those who were allowed to follow their own course. The work of Davis and his co-workers[7] on uterine tone and motility showed that some primiparas and most multiparas tend to exhibit irregularities. It is at the time of these irregularities which are unpredictable that the complications of involution may develop, chiefly post-partum hemorrhage and retention of lochia favoring puerperal sepsis. It seems reasonable to assume that if these irregularities can be prevented by the routine administration of a nontoxic drug such as ergonovine, the complications which may arise from the irregularities of tone and motility will be prevented. It may be that it would be advantageous to administer the drug over a longer period of time during the puerperium, not with the idea of hastening involution, but with the intention of keeping the involution of the uterus at a regular rate of progression until the uterus has returned to normal size. A case in point is that of a para iii who developed post-partum hemorrhage from subinvolution on the twenty-first day of the puerperium. It may be conjectured that if she had been receiving an oxytocic up to this time the emergency would not have developed. Further work on the toxicity of ergonovine over prolonged periods of administration must be done before such therapy can be advised.

I would like to propose the hypothesis that many uteri do not have the ability to maintain adequate tonic contraction for one reason or another; that there is thus a lag in the effectiveness of the contractions, a lag behind the rate that the organ is undergoing atrophy. Following evacuation of the placenta many injured blood sinusoids are left exposed on the inner wall of the uterus. Experience has shown how brisk the bleeding from these vessels may become. Compression of a bleeding blood vessel is a fundamental surgical principle in the control of hemorrhage. Compression of these exposed vessels is accomplished more or less by the rhythmic motility and contraction of the uterus which continues after delivery. But while the uterus is carrying on its rhythmic contraction, it is also undergoing a tremendously rapid atrophy. The atrophy is a process of catabolism of the individual cells of the myometrium whereby the cells become smaller in all dimensions, but chiefly in breadth. The contraction of the uterus, however, is due to a shortening of the fibromuscular cells in their longitudinal diameter. It is this shortening which exerts the effective pressure on the open sinusoids and prevents bleeding until the vessels have firmly thrombosed. If the contraction of the cells of the myometrium is not frequent and persistent enough to take up the slack produced by the process of atrophy, a relative flaccidity of the uterus is allowed to develop. Thus the effect of compression of the bleeding blood vessels is lost. The process may vary in degree so that the bleeding which is allowed to occur may be only the oozing which forms "lochia" or may be actual hemorrhage. It may be

inferred that the effect attempted in the use of an oxytocic is to assist this deficiency in tone and to maintain a rhythmic contraction of the uterus sufficient to keep pace with the atrophy of the organ.

CONCLUSIONS

1. The prophylactic administration of ergonovine in the form of ergotrate (Lilly) over several days in the post-partum period:

a. Increases the rate of involution of the uterus;
b. Produces a more regular rate of involution with fewer periods of greater or lesser subinvolution;
c. Results in a decrease in the amount of and the sanguineous nature of the lochia;
d. Reduces the puerperal morbidity due to uterine infection.

2. The rate and extent of involution in multiparas closely approximates that of primiparas when ergonovine is administered during the first three days of the puerperium.

3. The use of ergonovine in the post-partum period as prophylaxis is particularly beneficial in multiparas.

4. Normally multiparas have a less rapid and less regular rate of involution than primiparas.

5. Afterpains are, contrary to the usual belief, quite common in primiparas.

6. Ergotrate, in the dosage used in this study, increases only slightly the incidence of afterpains.

7. The prophylactic use of an oxytocic in the post-partum period is based on the fundamental surgical principle of hemostasis by compression.

SUMMARY

1. The effect of the routine administration of ergonovine during the first three days of the post-partum period was studied in 200 obstetric patients, primiparas and multiparas. One hundred patients were given the drug and 100 patients were used as controls.

2. The prophylactic use of ergonovine in the puerperium resulted in an increase in the rate and extent of involution, in a decrease in the amount and sanguineous character of the lochia, and in a decrease in puerperal morbidity due to uterine infection.

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A STUDY OF 1,200 CASES OF HYSTERECTOMY*

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REMOVAL of the uterus constitutes a large percentage of the surgery in the Department of Obstetrics and Gynecology at the Evanston Hospital. The operation is done for varied findings and many symptoms. Since several types of procedure are employed, we have felt that a study of our work would be of general interest and should enable us better to evaluate our results.

During the period October, 1929, to Jan. 1, 1940, we have done 1,200 hysterectomies. Of these, 744 were subtotal, 93 were total abdominal, and 363 were vaginal operations.

It is of interest that of the 363 vaginal hysterectomies, 275 have been done in the last five years, and that none were done the first year included in the study (1930). The peak of this incidence was the year 1937. Added experience, improvement in technique and the encouraging results reported from other clinics influenced us in our frequent selection of the vaginal route. It is impossible to have hard and fast rules governing the choice of operation, but excluding cases of known uterine cancer, residues of pelvic infection, adnexal pathology which must be dealt with otherwise, extremely large tumors and postoperative adhesions, our choice is usually the vaginal operation.

This operation is especially adapted to women in whom there is some relaxation of the pelvic floor and supporting structures, and in the presence of cervical disease and retrodisplacement. It lends itself to the repair of this relaxation by doing either anterior or posterior colporrhaphy, or both, and, of course, does away with the cervix. In the presence of complete prolapse and in those patients in whom the uterus protrudes only partially from the introitus, the interposition of the broad ligaments beneath the bladder, following the removal of the uterus through the vagina, has given us satisfactory results in most cases.

In some clinics the Manchester operation is preferred. One member of our group is using it now more often than formerly. It may well be that we have not accorded it the place it deserves. This, however, is a report on hysterectomy and is intended to show what we have been able to accomplish with that operation.

We regularly employ the total abdominal operation in known cases of carcinoma of the corpus. We have no knowledge of carcinoma appearing in the cervical stump in any of the 744 cases of subtotal hysterectomy included in this report. More important, however, is the fact that the pathologist discovered early cancer of the uterus in 18 patients

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in whom the cervix had been allowed to remain. A more routine use of the total procedure would have given these women additional protection. For the period as a whole only one out of nine abdominal operations has included the removal of the cervix. I wish to point out that this ratio is changing rapidly. In 1939, we did exactly twice as many total operations as in 1938.

Of these 1,200 women, 901 were multiparas and 299 were nulliparas. Of the 363 vaginal hysterectomies, 348 were multiparas and 15 were nulliparas.

The chief symptoms complained of in the order of their frequency were: vaginal bleeding, 711 (60 per cent); pain and discomfort, 471 (30 per cent); backache, 243 (20 per cent); leucorrhea, 154 (14 per cent); urinary disturbance, 141 (12 per cent); pressure, 49 (4 per cent). One hundred fifty-four either noticed enlargement or their physician had discovered a tumor. Seventy-seven (6 per cent) complained of a protrusion from the vagina and 34 (3 per cent) complained of a loss of weight.

TABLE I. AGE INCIDENCE

Under 21 years	4
21 to 30 years	57
31 to 40 years	450
41 to 50 years	503
51 to 60 years	113
61 to 70 years	58
Over 70 years	15

Because it is unusual to remove the uterus in a patient under 21 years, I wish to say that two of these girls, aged 17 and 19, had large degenerating fibroid tumors of the uterus. The uterus could not be saved. The remaining two, both aged 19 years, had residues of pelvic infection; their symptoms of pain and bleeding, and the presence of old inflammatory masses, brought them to operation. Both ovaries were preserved in the first two cases, and one ovary each in the other two.

TABLE II. INDICATIONS FOR OPERATION

INDICATION	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Fibroids	460	48	124
Functional bleeding	84	9	18
Prolapse	0	0	114
Pelvic inflammatory disease	61	9	0
Descensus and relaxation	0	0	67
Retroversion	24	0	32
Carcinoma	23	17	7
Ovarian cysts	25	5	0
Endometriosis	16	2	0
Postoperative adhesions	13	0	0
Tuberculosis (pelvic)	6	0	0
Tuboovarian abscess	6	0	0
Bilateral dermoid cysts	5	0	0
Twisted ovarian cysts	2	0	0
Ectopic pregnancy and fibroids	2	0	0
Pregnancy and multiple fibroids	2	0	0
Brenner tumor of ovary	1	1	0
Uterus perforated with curette	2	0	0
Fibroma of ovary	2	0	0
Sarcoma and sarcomatous degeneration	7	0	0
Bicornate uterus	1	0	0
Squamous cell carcinoma of cervix	1	2	1
Hydatidiform mole	1	0	0

TABLE III. PREVIOUS GYNECOLOGIC OPERATIONS

TYPE OF OPERATION	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Bilateral oophorectomy	3	2	0
Bilateral salpingectomy	18	1	0
Unilateral oophorectomy	47	5	4
Unilateral salpingectomy	27	1	4
Uterine suspension	46	10	9
Vaginal plastic operations	23	1	17
Exploratory laparotomy	7	0	0
Removal of ovarian cysts	13	4	0
Radium therapy	7	8	0
Ectopic pregnancy	5	2	2
Removal of tumors (myomectomy)	7	4	1
Amputation of cervix	9	4	0
Sterilization operation	4	0	0
Hysterotomy	3	0	0
Drainage of abscess	4	0	0
Repair of vaginal fistula	2	0	1
Resection of ovary	3	0	0
Transposition operation	0	0	2
X-ray therapy	0	5	0
Diagnostic dilatation and curettage	37	12	0

TABLE IV. ADDITIONAL OPERATIVE PROCEDURES

PROCEDURE	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Bilateral oophorectomy	157	39	4
Bilateral salpingectomy	177	39	5
Unilateral oophorectomy	199	11	7
Unilateral salpingectomy	162	9	5
Appendectomy	227	15	1
Anterior colporrhaphy	24	4	114
Posterior colporrhaphy	62	4	256
Diagnostic dilatation and curettage	19	10	12
Ovarian cysts removed	13	0	4
Bartholin cysts removed	0	0	2
Cervical plastic	33	0	0
Resection of ovary	16	0	0
Herniotomy	6	0	0

The bladder was opened three times while operating abdominally and twice while doing vaginal hysterectomy. Careful closure and the use of a retention catheter for some days resulted in satisfactory healing.

The bowel was opened three times while doing difficult dissections in the pelvis and twice while doing posterior colporrhaphy following vaginal removal of the uterus. With the exception of a fistula which remained open for six months in one of the subtotal operations, these patients made good recoveries.

Unless the operation is quite difficult and a stormy convalescence anticipated, or when much time has been consumed, we regularly remove the appendix. Two hundred forty-two appendectomies were done following the subtotal and total hysterectomies. Of the remaining cases many had previously had their appendices removed. Convalescence when appendectomy was done was no more stormy than when the appendix was allowed to remain. The average stay in the hospital was 15.4 days, and the morbidity of this group was 23 per cent.

The ten vaginal wound infections listed in Table V include only those of severe grade in which there was frank suppuration. I am sure that infection of the vaginal wound in a lesser degree accounts for much of the postoperative morbidity in this group.

In the treatment of complications, blood transfusions were given sixty times.

The average number of days spent in the hospital was 15.6. This does not represent the postoperative days. Many patients come in for examination several days before operation and this increases the average length of stay.

TABLE V. POSTOPERATIVE COMPLICATIONS

COMPLICATION	SUBTOTAL	TOTAL (ABD.)	VAGINAL
Wound infection	12	3	10
Pelvic infection	12	2	4
Bleeding	7	1	7
Hematoma	3	0	2
Peritonitis	8	2	2
Pelvic abscess	4	0	2
Pyelitis	3	1	5
Pneumonia	3	0	1
Pulmonary embolism	4	0	0
Phlebitis	1	0	2
Psychosis	3	0	0
Bowel obstruction	2	1	0
Rectal abscess	2	0	0
Empyema	1	1	0
Rheumatic fever (acute)	1	0	0
Ventral hernia	1	0	0

TABLE VI. MALIGNANCIES

Fundus:	33 adenocarcinomas
	2 papillary adenocarcinomas
	1 squamous cell carcinoma
	5 sarcomas
	2 sarcomatous degeneration of fibroids
	1 polypoid adenocarcinoma
	1 chorionepithelioma
Ovary:	4 adenocarcinomas
	1 malignant parvilocular ovarian adenoma
	2 papillary adenocarcinomas
Cervix:	2 adenocarcinomas
	3 squamous cell carcinomas
Tube:	1 papillary adenocarcinoma

The morbidity for all cases, using the American College of Surgeons standard, i.e., a rise to 100.4° F. on any two days excluding the day of operation, is 34 per cent. For the subtotal group it is 28 per cent; for the total, 46 per cent; and for the vaginal, 42 per cent.

Twenty-one patients returned to us because of gynecologic complications. Twelve returned, following subtotal hysterectomy, 3 because of bleeding from the cervical stump. In these cases, the cervix was removed. Three more were operated upon for ovarian cysts, and 3 for genital prolapse. A Sturmdorf operation was done on another because of cervical disease. Two women returned in whom cancer was found. One was found to have cancer of the ovary, and the other, cancer of the retroperitoneal lymph glands.

Six patients have returned following vaginal hysterectomy, 3 because of late pelvic abscesses, which were drained, and 2 because of recurrent rectocele and cystocele. On one of them a modified Le Fort operation was done and on the other an anterior and posterior colporrhaphy.

Three patients who had been subjected to complete hysterectomy for corpus cancer returned with large pelvic masses. In 2 of these cases, the abdomen was opened again, but advanced carcinomatosis precluded further surgery.

In the complete series there were 6 deaths, giving a mortality rate of 0.50 per cent. As none of these deaths were in the total or vaginal hysterectomy groups, the mortality rate for those groups was zero. Thus the mortality rate for the subtotal group, in which all the deaths occurred, is brought up to 0.80 per cent.

A brief discussion of each fatal case follows:

CASE 1.—The patient, aged 33 years, was operated upon for myopathic bleeding and retroversion. There was postoperative bleeding. The wound was opened

eighteen hours later, and the abdomen found to be full of blood. The patient went into shock. Sutures were inserted around the cervical and broad ligament stumps, and two blood transfusions were given. She developed peritonitis and died on the fourth postoperative day.

CASE 2.—The patient, aged 37 years, was operated upon for fibroid of the uterus, endocervicitis, and perineal relaxation. Perineorrhaphy, cervical plastic and subtotal hysterectomy were done. The patient developed acute rheumatic fever, and died on the nineteenth postoperative day. Post-mortem examination revealed acute ulcerative endocarditis and fibropurulent pericarditis.

CASE 3.—The patient, aged 44 years, was operated upon for residue of pelvic infection. Dissection was difficult. She died on the sixty-ninth postoperative day of progressive infection.

CASE 4.—The patient, aged 42 years, was operated upon for fibroids. She died on the operating table, as the abdomen was being closed, of respiratory failure. All attempts at resuscitation were futile.

CASE 5.—The patient, aged 54 years, was operated upon for fibroids. She developed peritonitis and intestinal obstruction. An enterostomy was done, but the patient died on the twentieth postoperative day.

CASE 6.—The patient, aged 74 years, was operated upon for fibroids and ovarian cysts. She died on the fifth postoperative day of pulmonary embolism.

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DISCUSSION

DR. IRVING F. STEIN.—That no deaths occurred after either total or vaginal hysterectomy is indeed worthy of note and a 0.5 per cent mortality for the entire series is enviable.

Concerning indications for vaginal hysterectomy, I find complete agreement with our own. I am particularly eager to stress the exclusion of those women who have evidence of pelvic residues and postoperative adhesions.

That no cases of stump carcinoma appeared in a ten-year period out of 744 cases of subtotal hysterectomy is to me quite remarkable. I recently learned that in the Tumor Clinic of Michael Reese Hospital, 9 such cases were discovered in the past two years. In view of this finding, we have seriously considered the advisability of extending our indications for total hysterectomy. At Mayo Clinic, total hysterectomy is done 3.4 times as often as the subtotal. They had 538 total hysterectomies in 1938 with 4 deaths; 156 subtotal, with no deaths; 165 vaginal, with 1 death; and 9 Wertheim with no deaths. In Dr. Smith's series, subtotal was the majority group and in this group only was their mortality.

I should like to ask whether there were no ureteral injuries during or following hysterectomy. In total hysterectomy especially, there is danger of ureteral injury, particularly so in cases of intraligamentary fibroids.

DR. H. O. JONES.—In a recent annual survey made in our hospital, results somewhat similar to those reported by Dr. Smith were obtained. There has been a gradual increase in the number of patients treated by vaginal hysterectomy. In a comparable series of vaginal and complete abdominal hysterectomies, we found a marked difference in favor of the vaginal procedure, morbidity and hospital stay less, fewer complications, reduced discomfort, and no mortality. Measuring the discomfort by sedatives used postoperatively, the vaginal cases required 25 per cent less.

Pulmonary embolism still remains one of our most dreaded complications especially in abdominal surgery. I wish to ask Dr. Smith whether his patients are subjected to any procedures which have, as a purpose, the increase of the circulation, to reduce the likelihood of phlebitis and embolism. Do you make it a point of having your patients out of bed at an early date?

In looking over our patients with phlebitis and embolism, we have not found one after vaginal procedures. A similar observation was made by another member of this Society in a very large consecutive series of vaginal hysterectomies.

DR. CHARLES E. GALLOWAY.—In the community where we work we do not see any carcinomas of the cervical stump recurring in patients who have had subtotal hysterectomy. That does not mean there are none, but on the other hand we are so situated that we would be very likely to see most of them.

We are not inclined to insert drains in doing a total abdominal hysterectomy. In the series reported we opened the bladder five times and injured the rectum five times, but not with any great harm. Regardless of how much care we take it seems that once in a while we have an accident.

There are many men who think an appendix should be left alone if it is normal. In this country, however, where women as well as men are likely to find themselves in the future in places where medical attention will not be given promptly, we feel that if it is a favorable case and things have gone along all right through the hysterectomy the appendix should be removed.

We do not seem to be able to get rid of the febrile morbidity associated with vaginal hysterectomy. Forty-two per cent of our patients had fever following vaginal hysterectomy for more than two days, some of them fairly high fever. We are now making vaginal cultures of every vaginal hysterectomy that comes to the operating room to see if we can learn anything from such a study.

DR. SMITH (Closing).—We use no retention catheter except occasionally in a case of extreme retention. Neither do we drain in either total or vaginal hysterectomy. We do put a pack in place in the vaginal operation which remains for twenty-four hours. We inject pituitrin into the cervix as we start the vaginal operation.

In answer to Dr. Jones' question about pulmonary embolism, we do nothing to lessen the incidence. I do not know why the incidence is low. We allow our patients out of bed from the eighth to the tenth day, those who have had vaginal hysterectomies about the eighth day and most of those who have had abdominal hysterectomies around the tenth day.

Concerning Dr. Galloway's discussion about morbidity, I was sorry when I completed this study that I had not kept track of the number of days the patient was morbid. In a paper Dr. Richardson presented some years ago he stated that for morbidity to mean anything, one should know how long the patient was morbid. If a patient is morbid for a week or longer, the after-effects of this morbidity are likely to be much different and of greater consequence than of patients who have only two or three days of morbidity.

AN ANALYSIS OF THREE HUNDRED HYSTERECTOMIES

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THE cases considered in this paper have been taken in straight series without selection, except for the omission of a few operations which included cholecystectomy, from the Gynecological Service of the Hospital of the Woman's Medical College of Pennsylvania and from three Gynecological Services at the Woman's Hospital of Philadelphia. They represent the work of seven surgeons. For the purpose of classification as well as possible comparison, they have been divided into five groups, namely: Simple supravaginal hysterectomy, supravaginal hysterectomy with salpingo-oophorectomy where no pelvic inflammatory disease was evident, supravaginal hysterectomy with salpingo-oophorectomy where pelvic inflammatory disease did exist, supravaginal hysterectomy with or without salpingo-oophorectomy where minor operations also were done,

and panhysterectomy with or without salpingo-oophorectomy. Although in such a series there were a number of preoperative handicaps, such as diabetes, hypertension, secondary anemia, etc., these have been disregarded in the interest of simplicity, and the recorded postoperative morbidity and mortality given without reference to pre-existing hazards.

The main object of this analysis was the determination of the postoperative morbidity and mortality, interest centering in a comparison between those of supravaginal hysterectomy and panhysterectomy. But several other subjects claimed sufficient attention to be included in the discussion. Many of these details, as discussed in the next paragraph, are embodied in Table I.

TABLE I. DETERMINATION OF POSTOPERATIVE MORBIDITY AND MORTALITY

NO. OF CASES	TYPE OF OPERATION	AVERAGE AGE	COLOR		SEDIMENTATION TIME IN MINUTES	OPERATING TIME	APPENDECTOMIES	AVERAGE DAY OF DISCHARGE
			WHITE	COLORED				
79	Simple supravaginal hysterectomy	37	47	32	86	83	41	17
46	Supravaginal hysterectomy *without* pelvic inflammatory disease	40	30	16	72	74	11	17
96	Supravaginal hysterectomy *with* pelvic inflammatory disease	35	72	24	68	78	30	18
35	Supravaginal hysterectomy with *minor* operations	38	24	11	119	108	12	16
44	Panhysterectomy	50	40	4	122	96	3	18

ANALYSIS OF CASES

There were 79 cases of simple supravaginal hysterectomy, the ages of the patients ranging from 25 to 55 years. In this group 47 patients were white and 32 colored. The average sedimentation time was 86 minutes. In 41 cases appendectomy was done. The average operating time was eighty-three minutes—five to ten minutes longer than in the groups in which salpingo-oophorectomies were included but the appendix less frequently removed.

The group of supravaginal hysterectomy with salpingo-oophorectomy without pelvic inflammatory disease totaled 46 cases, 30 white and 16 colored, with an average age of 40 years. The average sedimentation time here was 72 minutes. Only 11 appendectomies were done and the average operative time was 74 minutes. The group of supravaginal hysterectomy with salpingo-oophorectomy, because of the presence of pelvic inflammatory disease, was the largest of all, numbering 96. This is probably explained by the fact that both hospitals concerned draw a large part of their ward patients from negro sections of the city. In the given group, 72 were colored patients and 24 white. The average age was the lowest of the five groups, being 35 years. The sedimentation time also was lowest, averaging 68 minutes. Operative time averaged 78 minutes, with 30 associated appendectomies. The smallest group comprised supravaginal hysterectomy in addition to minor operations. There were 35 of these with 12 appendectomies included. In this group, in contrast with the last, 24 of the patients were white and only 11 were colored. The average age was 38 years. Obviously the longest operating time occurred in this series. It was 108 minutes. Notwithstanding this, the average hospitalization was shortest in this group.

In the group of panhysterectomies, the average age was higher than that in any other group, being 50 years, explained, no doubt, by the greater percentage of carcinoma of the body of the uterus. Here 40 of the 44 patients were white. The sedimentation time averaged 122 minutes. In 7 cases the appendages were not removed. There were 3 appendectomies. The average operative time was 96 minutes, next longest to the time of the combined minor and major operations.

INDICATIONS FOR OPERATIONS

The most frequent indication for operation was myoma uteri. There were 252 such cases. An analysis by groups is given in Table II. Sixty-seven of these were associated with cystic ovaries and 6 with carcinoma of the fundus, a per-

TABLE II. INCIDENCE OF MYOMA UTERI

TYPE OF OPERATION	TOTAL CASES	MYOMA
Supravaginal hysterectomy	79	75
Supravaginal hysterectomy with salpingo-oophorectomy *without* pelvic inflammatory disease	46	39
Supravaginal hysterectomy with salpingo-oophorectomy *with* pelvic inflammatory disease	96	89
Supravaginal hysterectomy *with* or *without* salpingo-oophorectomy with *minor* operations	35	31
Panhysterectomy	44	13

Macafee gives his percentage of myomas as 69 in a total of 122 cases; Reed and Bell give 66.6 per cent for cases on which subtotal operations were done and 24.4 per cent for cases on which total operations were done.

centage of 2.5.* There were 22 cases of malignancy of the uterus or ovaries not associated with myomas, 5 cases of procidentia, 4 of adherent retroversion, 2 of ovarian cyst, 8 of pelvic inflammatory disease, 2 of tears of the fundus, 2 of adenomatous polyps of the uterus, 1 of a pregnant incarcerated uterus, 1 of pelvic tuberculosis, and 1 of dysfunctional uterine bleeding.

LABORATORY FINDINGS, ETC.

In the whole series, the average preoperative hemoglobin was 67 per cent. The average white blood count was 7,386. The blood Wassermanns recorded were 24 positive and 127 negative. This leaves a large percentage, occurring chiefly among the earlier cases of the series, unregistered. It should be noted also that sedimentation times referred to in an earlier paragraph were not done in all cases but totaled 121 for the whole series.

The youngest patient of all those operated upon was 23 years old, the oldest 70. The average day of discharge varied little from group to group and so may be given for the whole series. It was 17.2 days postoperative.

MORBIDITY

In a series of this size it is difficult to draw any striking conclusions concerning the postoperative morbidity as indicated by the temperature curves. It was worked out for each group separately in the following manner: The low temperatures for one week, beginning the day of operation, were charted and an average drawn by the method of finding the median (i.e., the middle number for the group under consideration) for each day. The same thing was then done with the high temperatures for the day. This method, rather than that of taking the simple arithmetic average, was decided upon as a more just estimate, since it did not give undue emphasis to a few very low or very high morbidities. It seemed, moreover, a more accurate and graphic method of presenting postoperative morbidities than that recommended by Reed and Bell, who considered a case morbid if she was kept more than twenty-one days in the hospital after supravaginal hysterectomy and more than twenty-five days after panhysterectomy;

*Cf. Grave's figure of 2.0 per cent and Kelly and Cullen's of 1.7 per cent.

or by Fullerton and Faulkner who divided their series into those cases whose postoperative temperatures never rose above 101° F., termed afebrile; those with one day of greater temperature; and those with several such days.

There were no marked differences in morbidity. Probably the morbidity in those patients who underwent partial hysterectomy which was due to infection between the layers of the broad ligaments was counterbalanced by that due to the less good preoperative condition of many of those who underwent total excision of the uterus who were older and, therefore, in general, less good operative risks. The fact that the morbidity as charted was rather lower in the group of double operations than in the others may, perhaps, be explained by the assumption that the preoperative condition here must have been considered especially good or such a prolonged procedure would not have been undertaken. It is easily understood that the morbidity of the group in which pelvic inflammatory disease was present should be greatest and most prolonged. The presence of a large percentage of appendectomies in the group of simple supravaginal hysterectomies seems to account, in part, for the higher temperature range there than might have been expected. An additional cause for this may lie in the more easily infected area about a cervical stump which has been peritonized over intervening tubal ends.

POSTOPERATIVE COMPLICATIONS

The discussion of morbidity is incomplete without special reference to definite postoperative complications. They have been listed by group and tabulated in Table III. It will be seen that the highest percentage of complications occurred among the patients who had had panhysterectomies, infected incisions leading in number. This may be slightly misleading, as any degree of stitch infection, however minor, was included. The next highest percentage occurred among the patients with pelvic inflammatory disease, demonstrating the added obstacle to a smooth convalescence presented by this reawakening of latent infection.

TABLE III. POSTOPERATIVE COMPLICATIONS

COMPLICATIONS	SUPRAVAGINAL HYSTERECTOMIES				TOTAL	PAN-HYSTER-ECTOMY
	WITH SALPINGO-OOPHORECTOMY			WITH MINOR OPERATIONS		
	SIMPLE	WITH P.I.D.	WITHOUT P.I.D.			
Infected incisions of any degree	3	5	1	1	10	6
Pelvic phlebitis	4	8	0	1	13	2
Phlebitis of legs	2	3	0	0	5	1
Peritonitis	0	1(f)*	1(f)	0	2	1(f)
Pleurisy	0	2	0	0	2	0
Pneumonia	2	0	0	0	2	1
Pulmonary embolism	0	1	0	0	1	1(f)
Bronchitis	2	1	0	1	4	0
Tonsillitis	1	0	0	0	1	1
Sinusitis	1	1	0	0	2	0
Intestinal obstruction	0	1(f)	0	0	1	0
Gastric dilatation	0	3(1f)	0	0	3	0
Myocarditis	0	0	1(f)	0	1	0
Cardiac failure	1(f)	1(f)	0	0	2	0
Cystitis	0	1	0	0	1	0
Pyelitis	1	0	0	0	1	0
Rectal abscess	0	1	0	0	1	0
Hematoma	0	0	1	0	1	1
Septic infection	0	0	1(f)	0	1	0
Secondary hemorrhage	1	0	0	0	1	0
Cellulitis of space of Retzius	1	0	0	0	1	0
Acute psychosis	0	0	0	1(f)	1	0
Percentage	24.0	30.2	10.8	11.4	19.1	31.8

*f, fatal.

The patients who underwent simple supravaginal hysterectomies showed more postoperative pelvic complications than did those who underwent associated salpingo-oophorectomies in the absence of pelvic inflammatory disease. This suggests a more ready origin of pelvic phlebitis when the adnexa are left in situ because of less uniform approximation of the peritoneal fold to the cervical stump and consequently more minute ooze and infection about that stump. Moreover, a large percentage of these patients were subjected to appendectomies, which increased the operating time, and, by this as well as by opening another possible channel of infection, apparently increased the incidence of postoperative morbidity. On the whole, pulmonary complications were more numerous following the supravaginal operations, thus corroborating the findings of Reed and Bell, but by no means duplicating their report, which holds pulmonary embolism responsible for one-third of the deaths following the subtotal operation.

MORTALITY

There was one death in the group of simple supravaginal hysterectomies, due to acute cardiac dilatation. Three deaths occurred in the series including salpingo-oophorectomy where there was no pelvic inflammatory disease. One of these was due to myocarditis, one to peritonitis, and one to septic infection. There were four deaths in the group including pelvic inflammatory disease, one of cardiac failure on the table, one of peritonitis, one of intestinal obstruction and peritonitis, and one of dilatation of the stomach. The only death in the series where minor operations were included was of acute psychosis in which the autopsy showed no cause of death. Among the panhysterectomies there were two deaths, one of peritonitis and pneumonia and one of pulmonary embolism.

SUMMARY AND CONCLUSIONS

This study was undertaken as a survey of the services mentioned, with the object of ascertaining the results over a space of ten years.

TABLE VI. MORTALITIES

NUMBER	GROUP	PERCENTAGE
1	Simple supravaginal hysterectomy	1.2
3	With salpingo-oophorectomy (no pelvic inflammatory disease)	6.5
4	With salpingo-oophorectomy because of pelvic inflammatory disease	4.0
1	With minor operations	2.9
	Total supravaginal operations	3.6
2	Panhysterectomies	4.5
11	Total mortality	3.7

It shows that hysterectomy, although an operation frequently performed, is by no means free from danger.

It suggests that, without complicating pelvic inflammatory disease, there is more pelvic postoperative phlebitis after supravaginal hysterectomy without salpingo-oophorectomy than with it.

It indicates also that the removal of the appendix is a procedure which adds considerably to the postoperative morbidity.

It re-emphasizes the hazards of operations on patients with pelvic inflammatory disease, even when this is chronic in type.

Although the series is not large, it seems to indicate that both primary morbidity and mortality are higher in panhysterectomy than in supra-

vaginal hysterectomy. Since it does not, however, take into consideration the delayed morbidity and mortality due to residual or subsequent lesions of the cervical stump, it, therefore, does not pretend to settle the problem as to whether subtotal or total hysterectomy is the operation of choice.

It is submitted, therefore, as a small contribution to the discussion of this subject.

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UTERINE BLEEDING IN THE LAST TRIMESTER OF PREGNANCY*

Its Diagnostic Significance and Treatment

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IT IS a matter of common knowledge that bleeding from the uterus, occurring in the course of the last trimester of pregnancy, is usually indicative either of placenta previa or of premature separation of the placenta. In both textbooks and contemporary literature, there is a strong tendency to differentiate these two conditions by the presence or absence of pain during the bleeding. When pain accompanies the bleeding, the syndrome is generally considered to be pathognomonic of premature separation of the placenta, while in the absence of pain the bleeding is held, with about the same degree of assurance, to be due to placenta previa. Since our experience at The Brooklyn Hospital has led us to opinions sharply at variance with these concepts, we are presenting an analysis of all patients with bleeding in the later months of pregnancy treated at this institution during a ten-year period.

Following Bill's reports of about ten or twelve years ago, showing drastic reduction of both maternal and fetal mortality by the employment of cesarean section, a radical departure from formerly accepted procedures, the pendulum of obstetric opinion has swung far toward the use of that procedure in all cases of placenta previa among multiparas and primiparas alike. There has, likewise, been a similar trend in the handling of the other large group with bleeding late in pregnancy, namely, premature separation of the placenta. With modern tendencies so definitely toward this rather drastic form of treatment, it would not seem amiss to direct attention to the fact that many of our painless bleeding cases were due to varying degrees of premature separation rather than placenta previa and thus amenable to more conservative forms of treatment.

*Read at a meeting of the Brooklyn Gynecological Society, February 2, 1940.

Just as the authors of textbooks and articles have emphasized the importance of absence of pain in placenta previa, so have they stressed its presence as pathognomonic of premature separation. In discussing premature separation of the placenta, Bland states in his book: "The chief local symptom is bleeding. This is invariably associated with intense abdominal pain. We are familiar with no condition complicating pregnancy associated with a picture so strikingly characteristic. . . . A vaginal examination in order to clinch the diagnosis is not necessary in the face of symptoms so highly suggestive." McGlinn and Harer of Philadelphia comment: "It is not safe to permit any woman in whom a diagnosis of abruptio placentae has been made to remain undelivered for any considerable length of time, even in the absence of clinical evidence of profuse hemorrhage." While the above quotations represent the more radical and extreme views expressed in textbooks and literature, nevertheless, the sentiment in all I reviewed, leaned very strongly in that direction. Particularly surprising was the almost unanimous preference expessed in textbooks for cesarean section in even moderate degrees of premature separation.

Just as painless bleeding was not invariably associated with placenta previa in our series, premature separation was not always accompanied by pain. Had we followed the policy of radical intervention early in the majority of our cases, we would feel that we had needlessly subjected a goodly number of patients to the added hazards inherent in the initial and subsequent cesarean sections. Nor does the added danger of abdominal delivery over delivery from below at the first section tell the whole story. Some of these patients will develop adhesions, intestinal obstruction, rupture of the scar and may die during or following operation for these conditions. It is only when this secondary mortality is added to the primary that we may be able accurately to compare results in delivery from above and below.

It has been the policy of our service carefully to individualize each case and use those methods in the handling of it which seemed best suited to that case. Many outstanding men feel that these cases demand immediate diagnosis as to the cause of bleeding and immediate institution of treatment. They state quite categorically that there is no expectant treatment of placenta previa or premature separation of the placenta. With neither of these opinions are we in complete accord. Frequently we abstain from examining a patient who has bled but is no longer bleeding, occasionally even for several days, thus allowing the patient to re-establish her hemic equilibrium. Some of these patients may even be safely carried to viability of the child. We cannot agree that cesarean section without vaginal examination is indicated in all instances of painless bleeding. While such examination should be done only after all preparations for transfusion have been completed, it will definitely differentiate between painless premature separation and placenta previa, and indicate the type of previa and the state of the cervix.

In practically all cases of premature separation, it is our practice to rupture the membranes and apply a tight abdominal binder. This simple expedient, by reducing the amount of amniotic fluid in the uterus,

allowing it to contract down more tightly around the baby, thus closing off open sinuses and exerting direct pressure on the placenta, has satisfactorily controlled the bleeding in the majority of our patients. It is surprising to note that some of the modern textbooks do not even mention this form of therapy. Irving, in advocating its use, gives Polak credit for introducing it to this country from Ireland in 1931. It has been in use in The Brooklyn Hospital, to my knowledge, since 1923. We have resorted to cesarean section and hysterectomy hardly at all, feeling that in a situation desperate enough to require this operation, the patient would probably succumb from such a formidable procedure more certainly than if more conservative measures were used. In commenting on hysterectomy following cesarean section in uterine apoplexy, Irving rather aptly remarks: "The logic is not apparent which impels one to perform an operation with a 20 per cent mortality so that he may convert it into another with twice the death rate."

The cases here reported were taken from a total number of 10,217 consecutive deliveries in the ten-year period from 1928 to 1937 inclusive. There was a total of 70 cases of bleeding in the last trimester of pregnancy. This gives an incidence of 1 in 146 deliveries. Of these 70 cases, 55 were due to premature separation of the placenta and 15 to placenta previa. Of these 55 patients, 12, or 27.2 per cent, were toxic. Multiparity did not seem to play any part in producing premature separation, as less than half our cases, 23, were multiparas.

In premature placental separation, maternal mortality is reported as varying from 3 to 20 per cent. In the present series there were 6 deaths, or 10.9 per cent. In any discussion of premature separation, it should be emphasized that in some instances the detachment is so slight as to require little, if any, treatment, while in others the lesion is so extensive that it presents one of the most serious problems encountered in obstetric practice. Of our 55 cases, 28 may be classified as slight or mild, 18 as moderately severe, and 9 as very severe. We have endeavored always to make such a differentiation as the treatment varies with the degree of detachment. The membranes were ruptured and a tight abdominal binder applied in 40 out of the 55 cases. Only one cesarean section, and this without hysterectomy, was performed in this series. This was resorted to as much for toxemia as for ablatio placentae. Though the detachment undoubtedly contributed to the death of this patient, the toxemia was the main factor. It may be of interest in view of our seemingly high maternal mortality, to append a table (Table I) used by Irving to show the mortality rates in such cases when treated by cesarean section.

TABLE I

AUTHOR	CASES	DEATHS	PER CENT
Willson	21	4	19.0
Brodhead	8	3	37.4
Williams	10	3	30.0
Fitzgibbon	4	1	25.0
Davis	29	4	13.8
Siegel	11	2	18.2
Average	83	17	20.5

Gross fetal mortality in premature separation of the placenta is, from the very nature of the condition and the oftentimes questionable viability of the baby, necessarily high. The average of the figures reported by six authors is 73 per cent. In our series it is approximately 71 per cent.

I have left until last the discussion of the relation of pain to bleeding in ablatio placentae, in the hope that it will remain longest in your memory. It is the only original feature of this discussion. Of the 55 cases of premature separation of the placenta here reported, 27, or 49 per cent, had no pain at all either with or following the initial bleeding until the onset of labor pains. This, we feel, is a sufficiently large proportion of any obstetric complication to warrant emphasis and study. In 8 of these 27 cases, the bleeding occurred after the onset of labor but was not accompanied by any change in the character of the pains. In 8 other cases of the 27 painless separations, the condition was of sufficient gravity to warrant more than ordinary thought and concern. In 6 cases, the uterus was either tender, spastic or both, before their labors were completed. One of the 6 patients required transfusion and 1 died, showing that even the desperately ill may lack this symptom of pain, ordinarily considered a necessary feature of this entity. In 4 of the 27 cases, the hemorrhages were of the so-called concealed variety. The majority of our cases of painless separation presented a real problem in diagnosis, as the bleeding was the only indication that anything was wrong. The differential diagnosis was made by inability to palpate the placenta on vaginal examination and was later confirmed by evidence of placental separation at the time of delivery. That the painless type of premature separation is not confined to the earlier part of the last trimester when both uterus and baby are small, but may occur just before or at term, is attested by the fact that 11 patients were calculated to be at term and their babies weighed 7 or more pounds at birth. Brief summaries of 3 cases illustrating our point may be of interest:

CASE 1.—A 34-year-old para ii in the eighth month of pregnancy had a profuse hemorrhage, not associated with pain, two hours before admission. She was packed and sent to the hospital. Labor pains began soon after admission. First vaginal examination disclosed a thick, soft cervix, dilated two fingers. A smooth mass was palpated inside and between the cervix and presenting part. The uterus increased in size, became tense and tender. Labor pains were of poor quality and morphine caused temporary cessation of the pains. Vaginal oozing continued. A second vaginal examination, done seven hours after the first, revealed a cervix 3½ fingers dilated, thin, and no placenta was felt. The membranes were ruptured and delivery soon ensued. About one quart of old, dark blood clots was expelled. Approximately half of the large placenta showed evidence of detachment. The final opinion was that the mass felt on first vaginal examination was blood clot. The final diagnosis was premature separation of the placenta.

CASE 2.—A patient, 34 years of age, a para iv, in the seventh month of pregnancy, had profuse bleeding before admission, but no pain, tenseness, or tenderness of the uterus. She was immediately transfused. Vaginal examination showed no placenta previa. The membranes were ruptured. No pains occurred for eleven days. At that time a rapid labor occurred with spontaneous delivery, the baby weighing 3 pounds 4 ounces. Large blood clots adherent to the central portion of the placenta indicated detachment at that site.

CASE 3.—A 20-year-old primipara, eight and one-half months pregnant, was admitted to the hospital one hour after the occurrence of moderate hemorrhage, without pain. The admission diagnosis was placenta previa. Examination by an attending obstetrician two hours after admission revealed a slightly tense, irritable uterus with a tender area 2 by 3 inches in the left lower quadrant, but without pain. Vaginal examination showed no evidence of placenta previa. The membranes were ruptured and a tight abdominal binder applied. Labor began two hours later with no further bleeding. Spontaneous delivery occurred five hours after rupture of the membranes. Several old blood clots were present on the maternal surface of the placenta.

SUMMARY AND CONCLUSIONS

1. It is our opinion that all patients with bleeding should be examined vaginally before cesarean section is done. This examination will definitely differentiate between placenta previa and painless premature

separation of the normally implanted placenta, frequently indicating less radical treatment than cesarean section.

2. We believe that premature separation of the placenta is usually better treated by the more conservative method of rupturing the membranes and application of a tight abdominal binder than by cesarean section.

3. We have endeavored to show that the widely accepted dictum that painless vaginal bleeding in the latter months of pregnancy is almost always indicative of placenta previa, is fallacious. Of 41 cases of painless bleeding here reported, 27, or 60.6 per cent, were due to premature separation of the placenta, rather than placenta previa.

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DISCUSSION

DR. CHARLES A. GORDON.—Our experience with placenta previa has been entirely different from the experience of those at The Brooklyn Hospital.

I have recently reviewed 44 cases of placenta previa which occurred on the College Division at Kings County Hospital in the last five years. In all but 5 of these cases the history was the typical one of painless bleeding. In three of these 5 cases, pain was associated with the onset of labor. This is an entirely different picture.

The incidence of placenta previa on any service is of very little significance, for it varies for a great many different reasons. Incidence is unimportant. That placenta previa may be associated with pain is clear; that patients with separation may have no pain is clear. The separated placenta previa confuses the clinical history and the clinical picture. Low implantation of the placenta gives an atypical history, but for practical purposes it is placenta previa.

If the diagnosis is to depend upon palpation of the placenta, some cases will be missed. If the diagnosis is to be made on the history alone, that history must be very carefully taken and carefully weighed. It will be difficult to establish the thesis that the history of placenta previa is not that of painless bleeding in the last trimester.

THE SUPPRESSION OF LACTATION BY STILBESTROL*

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INHIBITION or suppression of lactation in the puerperium is frequently necessary. This procedure is usually prolonged, painful, and occasionally is difficult to accomplish. Recently we have employed a synthetic estrogenic substance for this purpose with satisfactory results.

We have administered stilbestrol orally to 75 puerperal women for the purpose of suppressing or inhibiting lactation. The duration of the pregnancies is shown in Table I.

TABLE I. DURATION OF PREGNANCIES

0-21 weeks	3
22-28 weeks	6
29-37 weeks	9
Over 37 weeks	57
Total	75

The indications for the suppression of lactation are shown in Table II.

TABLE II. INDICATIONS FOR SUPPRESSION OF LACTATION

Insufficient lactation	22
Elective	19
Neonatal death	11
Stillbirth	11
Inverted or tender nipples	6
Abnormal milk	2
Sick baby	2
Eclampsia	1
Maternal tuberculosis	1
Total	75

The majority of these women were private patients, and the indications listed are those given by the physicians in charge. Insufficient lactation was the reason given most frequently for drying the breasts. A number of these patients were able to provide only from one-half to one ounce at each nursing, but had firm and painful breasts. These women were considered as having "insufficient lactation." While such breasts can often be dried by the usual methods without great difficulty, the patients are more comfortable and the period of lactation is shortened if stilbestrol is employed.

The number of days following delivery before the administration of stilbestrol was started is shown in Table III.

*Read at a meeting of the Philadelphia Obstetrical Society, March 7, 1940.

TABLE III. TIME FOLLOWING DELIVERY

DAYS AFTER DELIVERY	NO. OF PATIENTS
0-3	33
4-7	22
8-14	17
15-28	3

An arbitrary dose of 5 mg. of stilbestrol by mouth 3 times a day for a total of six doses was employed. The patients were encouraged to drink liquids freely. Tight breast binders were not employed, laxatives were ordered only for constipation, and the time-honored application of warm camphorated oil was omitted.

RESULTS

Our results following this routine were indeed gratifying. In no case did the breasts fail to become soft within twenty-four to thirty-six hours if lactation had commenced. The usual tenderness and pain were less pronounced and of shorter duration than with the older routine, consisting of tight binding of the breasts, saline catharsis, restricted fluids, and warm camphorated oil. In a few instances, a slight amount of secretion could be expressed at the expiry of this time. If medication was started the day after delivery, filling of the breasts could often be prevented.

We were able to follow 53 of our 75 patients for a sufficient length of time to determine the number of women in whom some degree of lactation reappeared. With the technique employed, 40 per cent of these patients had some return of lactation, usually on the fourth or fifth day after the last dose of stilbestrol. When lactation reappeared, there was less engorgement and the amount of secretion was small. These patients were given a second course of stilbestrol, 5 mg. three times in one day, and this usually sufficed to suppress lactation permanently.

Each patient in this series received a total of 30 mg. of stilbestrol within thirty-six to forty-eight hours. Two other patients (not included in this series) received 10 mg. three times a day for a total of 60 mg. Only two patients were nauseated, and these were both on the smaller dosage. In neither instance was it necessary to stop the administration of the drug. No other untoward effects were noted.

SUMMARY

Stilbestrol has been used in a series of 75 puerperal women for the purpose of inhibiting or suppressing lactation. Five milligrams of stilbestrol administered three times a day for a total of 6 doses relieved the breast engorgement, and decreased or prevented lactation in every case. In 40 per cent of 53 patients followed, there was a secondary recurrence of lactation. This was usually painless and slight in amount. Only 2 patients were nauseated in a series of 75 women receiving stilbestrol. We feel that the use of stilbestrol is an efficient and safe method of suppressing lactation early in the puerperium.

We wish to thank Dr. J. A. Morrell of E. R. Squibb & Son for supplying the stilbestrol used in this study.

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STILBESTROL IN THE TREATMENT OF MENOPAUSAL SYMPTOMS*

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THE clinical effects of stilbestrol have been reported in more than one hundred publications. These reports confirm the estrogenic properties of the substance but many of them question the safety of its therapeutic administration. Our experience further attests to its clinical effectiveness and casts doubt upon its potentialities of harm, provided it is administered conservatively.

We have used stilbestrol by oral administration in a series of 52 patients who were suffering from climacteric symptoms. There were 16 whose treatment was temporarily suspended for a number of weeks, to be resumed later. This enables us to present the results of 68 courses of treatment which varied from one to six months in duration. The patients were classed into three groups, according to the origin of the menopausal symptoms: (1) Those still having menstrual periods. (2) Those with spontaneous menopause. (3) Those with surgical or radiologic menopause. In this study we used the relief of flushes as the criterion of therapeutic effectiveness. Other general and local reactions were noted and recorded. Efforts were made to determine the minimal effective dose and to identify any untoward or toxic reactions.

It became apparent quite early that comparatively small doses were adequate. The requirements for relief seemed to vary according to the origin of the menopausal reaction. In the group in whom menstruation had not ceased, although climacteric symptoms had begun, mild doses of 0.1 mg. to 0.3 mg. per day usually were effective. For the spontaneous menopause group, the requirement increased to 1.0 mg. a day. The cases of radiologic or surgical menopause not only presented the most severe symptoms but needed the largest doses, usually requiring from 1.0 to 3.0 mg. a day (Table I).

Following an adequate initial dose, symptomatic improvement usually occurred within from four to seven days. The duration of treat-

*Read at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

TABLE I. CLINICAL RESULTS

	NO.	RELIEF	PARTIAL RELIEF	NO RELIEF	USUAL DOSE
Menstruating	13	8	3	2	0.1 to 1 mg.
Spontaneous menopause	17	13	3	1	1 mg.
Surgical or radiologic menopause	38	26	5	7	1 to 3 mg.
Total	68	47	11	10	
Per cent		69	16	15	

ment varied according to the severity of the symptoms and the nervous stability of the patient. Occasionally, permanent relief followed treatment of four to eight weeks' duration. More often it was necessary gradually to diminish the dose over a period of weeks until estrogen was no longer required and mild barbiturates maintained comfort.

SIDE EFFECTS

As to the local effects of the drug, an estrus or squamous type of vaginal epithelial response appeared usually, although the relief of flushes occurred frequently at lower dosage than did the vaginal changes.

Recurrence of vaginal bleeding appeared in 11 patients who had previously stopped menstruating. This followed relatively large doses of the substance as a rule, and we believe that a happy medium usually can be found between the relief of flushes and recurrence of bleeding. In no instance did the bleeding persist following cessation of therapy, and no case of malignancy was observed.

The general side effects were not startling. Little alteration was observed in the blood pressure or pulse rate. The common menopausal complaint of insomnia usually was relieved. The libido was unaltered. Preexisting vertigo was not affected, nor did the drug produce vertigo. While constipation was relieved by correction of the bowel habits, our experience indicates that stilbestrol acts as a mild laxative. The general relief of the subjective symptoms was accompanied by an improvement in the appetite and not by the development of anorexia, nausea, or vomiting. The majority of the patients stated that they felt greatly improved, and many returned voluntarily for further medication after a lapse in treatment was followed by the recurrence of menopausal symptoms.

TOXIC REACTIONS

The general acceptance of stilbestrol, which possesses the attractive features of inexpensiveness, ease of administration, and effectiveness, has been delayed because of its possible toxicity. The reports in the literature are widely divergent upon this point. The majority of investigators have not encountered a large percentage of untoward reactions. Reports of examinations of the blood and urine, and liver function tests usually have failed to reveal any deviation from normal.

The recent report of the Council on Pharmacy and Chemistry of the American Medical Association contains the following statements:

"The reports . . . have indicated that for the most part the toxic reactions of stilboestrol were limited to gastro-intestinal distress in from five to fifteen per cent of the patients treated." . . . "Because the product is so potent and because the possibility of harm must be recognized, the Council is of the opinion that it should not be recognized for general use at the present time."

In our series, nausea and occasional vomiting occurred in 7 (10 per cent) of the 68 courses of treatment. This low incidence of gastro-

TABLE II

DAILY DOSAGE		CLIMACTERIC SYMPTOMS
DOSAGE MG.	NUMBER TREATED	TOXIC REACTION
0.1	9	1
0.2	5	1
0.3	6	0
0.5	3	0
1.0	35	4
2.0	10	1
Total	68	7

intestinal disturbance probably is due to the use of much smaller dosage than that which has been employed previously. None of our patients developed skin lesions, or exhibited signs of liver damage, although liver function tests were not done. There was no diarrhea, and no other deleterious effects were noted.

SUMMARY AND IMPRESSIONS

Stilbestrol has been administered to a series of 68 patients suffering from menopausal symptoms. Forty-seven (69 per cent) obtained complete relief, 11 (16 per cent) partial relief, and 10 (15 per cent) were not relieved by the administration of the drug. Seven (10 per cent) of the patients developed nausea or vomiting. Based upon this modest number of observations, we have gained the following impressions: Stilbestrol is estrogenic, and small quantities relieve climacteric symptoms rapidly and efficiently in the majority of patients. The most effective doses for this purpose range from 0.1 to 1.0 mg. per day. While a limited number of patients cannot tolerate stilbestrol, this intolerance appears to be manifested by minor gastrointestinal disturbances and not by major or permanent toxic effects, provided the dosage is restricted to the minimal effective requirements.

We wish to thank Dr. J. A. Morrell of E. R. Squibb and Son for supplying the stilbestrol used in this study.

DISCUSSION ON PAPERS BY MUCKLÉ, AND MUCKLÉ AND PAYNE

DR. HOWARD C. TAYLOR, JR.—The 15 per cent of reported failures in the menopausal cases are of interest. This seems to me a little higher than one might expect with the natural estrogens. I would like to know whether any studies were made to determine the reasons for the failures. Did the vaginal

smears change in these cases; did the gonadotropic substance disappear from the urine; and, finally, was it possible to overcome the 15 per cent of failures by the use of any other type of estrogenic substance?

There seems to be little doubt that stilbestrol tends to diminish lactation. Since these women discontinued nursing at the same time that the medication was begun, there were, however, two reasons for the cessation of lactation, namely the discontinuance of the stimulus to the nipple, and the drug. The fact that the lactation returned in some patients after the discontinuance of the stilbestrol is certainly an indication that the drug itself played a large part. It would however, be interesting to know if the amount of secretion could be diminished if the child continued nursing or the breasts were pumped.

The convenience and cheapness of this drug, as well as the clinical reports of its efficiency, recommend it above all the other estrogenic substances available for clinical use. The single obstacle appears to be the possibility of its toxicity, which holds up its immediate acceptance.

DR. CHARLES MAZER.—Drs. Payne and Mucklé's observations are in the main in accord with my clinical observations on the use of stilbestrol in nearly 200 patients.

The product has the physiologic attributes of the natural estrogens and has a potency of 5,000 rat units per milligram. It is more potent when given orally than any other available estrogenic substance.

We have approached the problem of toxicity both experimentally and clinically. Clinically, we found no changes in the weight, blood pressure, basal metabolic rate, urine and blood constituents in 10 completely studied patients who have received the product over a period of three months in relatively large doses. The cholesterol content of the blood rose to an abnormal height in 2 of the 10 patients. Nausea and vomiting follow the administration of large doses, such as 2.0 mg. daily, in about 25 per cent of the patients.

Experimentally, the administration of 1.0 mg. daily for forty-two days produced no changes in any of the organs of the rabbit, but 3.0 mg. daily for forty-two days produced definite necrotic changes in the liver, spleen, and kidneys. In the rat, 0.1 mg. daily for an equal length of time produced congestion of the vital organs, and 1.0 mg. daily produced definite necrotic changes in the liver, spleen, and kidneys.

There is no doubt that stilbestrol has a much higher toxicity than the natural estrogens when the dose is computed in terms of weight and not in terms of rat units.

DR. S. LEON ISRAEL.—Drs. Payne and Mucklé's paper is one of the first on stilbestrol, which comments on the importance of using small doses.

In support of the clinical effectiveness of small quantities of stilbestrol are our own studies on castrated women at the Mount Sinai Hospital. We were interested to determine just what quantity of stilbestrol the castrated woman requires to maintain her blood and urine estrogen-content at the normal premenstrual levels. Our current investigations in 12 surgically castrated women indicate that as little as 0.1 mg. of stilbestrol taken orally twice daily maintains the blood level of estrogen at 1 M.U. per 40 c.c., and the urine level at from 15 to 20 R.U. per twenty-four-hour output in a castrated woman. This observation seems to support the viewpoint stressed by Drs. Payne and Mucklé that small doses of stilbestrol are not only less toxic but clinically effective.

DR. PHILIP F. WILLIAMS.—Drs. Shemkin and Grady of Washington gave a demonstration of the comparative effects of estrin and stilbestrol in the production of mammary cancer in susceptible mice. By the oral route stilbestrol was six times as potent in producing mammary carcinoma as the estrin. By the percutaneous route the stilbestrol was twice as potent as the estrin. According to their figures for the mouse they consider that to produce carcinoma in the human breast you would have to give 3,000,000 units once a week for twenty years if an equivalent carcinogenic effect was needed.

DR. A. E. RAKOFF.—The chief question that arises in regard to stilbestrol concerns the possible toxicity. The reports concerning its use indicate a wide variation in observed toxic effects. In our own experience, which includes observations on about 100 patients, we feel that 75 per cent can take the drug in moderate dosage without ill effect, and that the majority of the remainder will tolerate the drug after an initial period of nausea and headache.

One of the reasons for the wide prevalence of toxic effects is that too large a dose is frequently given. It should always be borne in mind that stilbestrol is a highly effective estrogen and that only in special instances is it necessary to give more than 1 mg. daily. Most patients could not afford to take an equivalent amount of a natural estrogen.

From our observations we have gained the impression, however, that a few patients have a distinct susceptibility to stilbestrol. The most severe reaction which we have found in two patients, for which no other cause could be found by the proctologist, was unexplained rectal bleeding. Another peculiar type of reaction was found in 2 patients who were receiving treatment with natural estrogens. When stilbestrol was occasionally substituted without their knowledge, they complained of severe headache and depression, and a sensation of being "drugged." They were always able to tell when they received stilbestrol rather than a natural estrogen.

A number of children with gonococcal and nonspecific vaginitis, whom we have treated with stilbestrol in a dosage of 0.2 to 1.0 mg. daily, tolerated the drug very well. There were no toxic reactions in any instance. The best therapeutic results were obtained when the drug was given in suppository form.

DR. WALT P. CONAWAY.—At a meeting of the Central Society for Clinical Research held in Chicago in November, 1939, Dr. Sevringhaus of Madison, Wisconsin, stated that with stilbestrol it was possible to get complete relief in each case tested by the oral administration. Dr. Frank Allen, of the Lahey Clinic, reported that they had used stilbestrol in 45 cases. Of his 26 carefully analyzed cases, there was definite relief in 24, but in 2 cases treatment was discontinued on account of mild toxic symptoms, such as nausea, rarely vomiting, but occasionally abdominal discomfort and marked general malaise.

DR. MUCKLÉ (closing).—Of the 68 courses of treatment, failure to obtain relief of symptoms occurred in ten instances. Seven of these failures were due to gastrointestinal symptoms which prevented maintenance of adequate dosage. In the other 3 cases, the amounts administered were insufficient in the light of our present knowledge. It is our impression that clinical relief could be obtained in every case if adequate therapy could be maintained.

Delannoy, E., and Demarez, R.: Tumors of the Internal Genitalia Among Prepubertal Girls, Compt. rend. de 8 nne Congres, Franç. de gynéc. **30**: 135, 1939.

There has not been a single report of a benign or malignant tumor of the Fallopian tube in a child. On the other hand there have been many reports of cysts of the ovary, the most common neoplasm of the genitalia in young girls. Other tumors which occur in young girls are solid tumors of the ovary, such as sarcomas, carcinomas, granulosa cell tumors, chorionepitheliomas, dysgerminomas and teratomas. Some of these neoplasms produce precocious sexual maturity. The treatment of these tumors is essentially surgical.

Tumors of the uterus in young girls before puberty are always malignant and they are rarer than ovarian growths. These uterine neoplasms consist of grapelike sarcomas of the cervix, ordinary sarcomas, squamous cell carcinomas of the cervix and adenocarcinomas. The treatment of these tumors is likewise surgical.

J. P. GREENHILL.

THE USE OF HELIUM AND OXYGEN IN THE TREATMENT OF ASPHYXIA NEONATORUM*

PRELIMINARY COMMUNICATION

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THE use of helium as a therapeutic gas was first suggested by Barach[1] in 1934, although in 1923 it had been employed in decompressing men working under high gas pressure.

The effectiveness of helium is due to the fact that the density of this gas is one-seventh that of nitrogen and one-eighth that of oxygen, and that it is an inert gas which can replace the inert nitrogen of air. A mixture of 80 per cent helium and 20 per cent oxygen is three times as light as air, and is, therefore, because of its greater diffusibility much more easily breathed. Barach has shown that such a mixture will pass through obstructed respiratory passages and into collapsed alveoli which are impenetrable by air.

Benedict, White, and Lee[2, 3] found helium-oxygen to be of benefit in the treatment of the respiratory failure frequently experienced by the newborn infants of diabetic mothers. They believe that every cubic centimeter of nitrogen in air is a liability and that it can be replaced, at least theoretically, by helium. After experimenting with mixtures of various proportions, these investigators decided that the most efficient combination was 80 per cent helium and 20 per cent oxygen. This provides as much oxygen as is present in air, and if more oxygen were used it would form a heavier, less diffusible mixture. The benefit, if any, of the increased amount of oxygen would be nullified by the decrease in the penetrability of the mixture.

In view of the findings of these observers, it seemed probable that if helium would carry oxygen into partially obstructed air passages and alveoli of functioning lungs, it would act similarly in the undilated lungs of asphyxiated newborn babies when supplied under properly controlled pressure.

In approximately 200 cases, the mixture of 80 per cent helium and 20 per cent oxygen has been employed. Few of these babies were deeply asphyxiated, some not at all. Because of the belief that every minute of delayed respiration may cause irreparable damage to brain tissue, every infant, immediately after the cord is cut, is placed in a respirator and oxygen or helium-oxygen is administered. The apparatus used is the Kreiselman modification of a resuscitator described in 1928 by Kreiselman, Kane and Swope,[4] which delivers gas to the upper end of the trachea under controlled pressure. Several methods of evaluating the increased efficacy of the mixture over undiluted oxygen have been tried, none of which gave information of value. The experi-

*Presented at a meeting of the Washington Gynecological Society, March 23, 1940.

ments by Barach[5] on human adults who were able to cooperate and on dogs which could be autopsied, could not be duplicated with infants as subjects. Barach's findings, based upon the study of functioning lungs, show unquestionably that helium-oxygen requires a markedly lower pressure to pass it through partially obstructed passages than do air or oxygen.

Barach[6] also notes that "with severe obstruction the inspiratory stridor is accompanied by a sucking in of the abdominal or chest wall." This phenomenon is commonly seen in partially asphyxiated infants. "In the presence of such marked inspiratory obstruction, the secondary development of edema fluid and red corpuscles passing into the alveolar sacs contributes the dangerous factor of severe anoxemia with its resultant damaging effect on the circulatory and respiratory systems. The use of helium as a diluent facilitates the entrance of the combined gas and tends to prevent fatigue and paralysis of the respiratory musculature." After respiration has been established, therefore, it is advisable to continue the administration of helium-oxygen until the chest movements denote that breathing requires only normal muscular action.

Belief in the clinical value of the 80 per cent helium and 20 per cent oxygen mixture in the resuscitation of the asphyxiated newborn is based wholly upon the observation, perhaps biased, of 200 babies by several of the attending staff, anesthetists, the house staff, delivery room supervisors, and nurses at Garfield Hospital. All agree that in cases of light asphyxia the babies respond much more quickly to the mixture than to pure oxygen. In several cases of deep asphyxia, after oxygen alone had been used without success, the addition of helium was followed by almost immediate clearing of cyanosis and prompt respiratory movements.

The author realizes that a theory based upon experiments of others which are not exactly relevant, and upon the clinical observation of a small number of cases is practically unsupported.

The suggestion that helium be added to oxygen as a medium for initiating respiration in the asphyxiated newborn is presented, however, in the hope of stimulating further investigation of its value.

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RENAL INSUFFICIENCY FOLLOWING TRANSFUSION OF COMPATIBLE BLOOD*

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THIS case is reported as evidence that renal insufficiency may follow transfusion of blood judged compatible by our present methods, and that the administration of alkalies as first recommended by Baker[1] to avoid this complication will not always do so. Although a few cases of renal insufficiency following the transfusion of compatible blood have been reported, it is not generally known that this may occur.

CASE REPORT

C. B., aged 30, gravida iii, para ii, was admitted to Kings County Hospital on May 31, 1939 with a history of being in active labor for five hours. Her past history was negative except for antisyphilitic treatment two years before admission.

After ten hours of active labor the patient delivered spontaneously a living full-term infant, followed by delivery of an intact placenta twenty minutes later. Profuse bleeding (about 500 c.c.) immediately followed, and despite the administration of oxytocics and vigorous message of the fundus, the patient showed signs of shock. A 500 c.c. citrated blood transfusion (Type IV Moss) was given slowly (cross matching compatible). At the same time 15 grains of sodium bicarbonate was given by mouth every four hours. One and one-half hours after the transfusion the patient complained of a severe headache followed by a chill. The temperature was 101°F. pulse 136 and blood pressure 110/70. Five hours after delivery a large blood clot was expressed and moderately profuse hemorrhage again occurred. Blood pressure dropped to 80/60 and 1000 c.c. of citrated blood was given by drop method, over a period of three hours. Seven hours after the first transfusion, the patient's temperature was 105°F. and she showed deep jaundice. The urine was alkaline and showed many red blood cells. Two hundred and fifty cubic centimeters of 5 per cent sodium bicarbonate were given immediately intravenously. A sample of each specimen of the blood given was saved and on cross matching was found to be compatible with the patient's blood.

During the next five days the patient voided 15 to 55 c.c. of dark amber urine daily, despite an intake of 3000 c.c. of fluids each day. The daily output and corresponding blood chemistry are shown in Table I.

TABLE I. RENAL INSUFFICIENCY AFTER TRANSFUSION OF 1,500 C.C. OF BLOOD

DAY	INTAKE C.C.	OUTPUT C.C.	UREA MG.	CREAT. MG.	ICTERUS INDEX UNITS	CO_2 VOL. %
First	2980	165	64	1.8	100	32
Second	2500	15	58	2.1	50	
Third	3000	45	58	2.5	25	88
Fifth	3000	55	115	3.8	21	55
Sixth	3000	1560	64	3.7	16	60
Seventh	4900	4110	125	6.0		
Eighth	3360	2980	120	6.0		
Tenth	5060	4525	80	5.0		
Eleventh	5945	4810	74	2.4		
Twenty-first	3360	2450	36	1.8		

The patient ran a temperature of 101° to 103° F. and on the sixth day post partum complained of pain in her right chest. X-ray examination revealed early bronchopneumonic consolidation. On the eleventh day post partum the patient began to have severe pains in her shoulder, later in her hip and knee joints.

*Read at a meeting of the Brooklyn Gynecological Society, February 2, 1940.

Fifteen days after the transfusion reaction the advisability of another transfusion was considered because of the patient's septic condition and hemoglobin of 30 per cent. After consultation with the Department of Medicine, the patient was given 500 c.c. of citrated blood without reaction. Four smaller transfusions were given at later dates without showing evidence of incompatibility.

Forty-five days post partum the patient continued to run an elevated temperature and showed evidence of a perirectal abscess. This was subsequently drained with remission of her temperature. The migratory polyarthralgia continued until discharge from the hospital. After three months the patient was able to walk but complained of intermittent pains in her knees and hips. X-ray examination three months post partum showed interstitial calcinosis occurring about the knee and hip joints. It is uncertain whether the transfusion reaction was responsible for this complication.

The blood transfused came from the hospital's blood bank, which has been functioning successfully since its introduction. Over 5,000 transfusions are given each year with a low incidence of reactions (7.3 per cent). The blood was cross matched by routine method, i.e., donor's cells with recipient's serum and recipient's cells with donor's serum. A competent technician is in charge of the cross matchings. The blood transfused was withdrawn from three separate donors three days prior to the transfusion. All donors were recalled after the reaction and the blood again showed compatible cross matching with the patient.

COMMENT

A few cases have been reported in which severe reactions followed the transfusion of compatible blood as determined by our present agglutination tests.

Our present method of determining compatibility is based on agglutination tests. Moss[14] stated in 1910 that "Iso-agglutination may occur independently of iso-hemolysis but iso-hemolysis is probably always preceded or accompanied by iso-agglutination." Kolmer[11] cites Moss as having later noted instances where the sera had contained hemolysins without agglutinins. Other writers later confirmed this observation.

Bernheim[2] was the first to report a case of hemolytic reaction without agglutination. Goldring and Graef[8] reported 7 cases of severe transfusion reactions and found that agglutination occurred in all but one case. De Gowin and Baldridge[5] in 1934 reported two fatal transfusion reactions with Type IV (Moss) blood, yet cross matching had been perfectly satisfactory. Johnson and Conway[10] have reported two similar cases. Gordon[9] in 1935 reported one case where cross agglutination of donor and recipient showed compatible blood, but grouping had not been done.

All the reported cases where grouping was done were Type IV Moss. In all cases there was no apparent relationship between the amount of transfused blood and the severity of the reaction. De Gowin[6] suggests that repeated transfusions increased the hemolytic tendency since, in the 4 cases he reviewed, the patients had repeated transfusions of varying amounts, all having had previous transfusions. The method of giving the blood does not seem to play a part in the reaction, for in the 2 cases reported by De Gowin[7] transfusions of whole blood were given, while in the 2 reported by Goldring and Graef[8] citrated blood was used. In our case no previous transfusion had been given and the patient had subsequent transfusions without reaction.

De Gowin and Baldridge[5] quoting experiments by Mason and Mann showed that hemoglobin had a vasoconstrictor effect on the kidney and state, "It is as yet not possible to say whether the vasoconstrictor effect or the blocking and destruction of the tubules is the more important." Although the exact mechanism of the anuria is still uncertain, death is due to complete or partial suppression of urine preceded by intravascular hemolysis of the donor's corpuscles and a typical kidney lesion in which Baker[1] and Bordley[3] summarize as follows:

1. A precipitate of hematin in the lower parts of the tubular systems extending, in some cases, into the secondary convoluted tubules.

2. Albuminous degeneration of the tubular epitheleum without necrotic or fatty changes but with desquamation of some of the cells into the tubular lumina.

3. A variable degree of general dilatation of the tubular systems which may be marked and also involve Bowman's capsules.

4. No signs of inflammation or other significant lesions in the glomeruli.

5. As a late result a varying amount of edema and possibly chronic inflammatory infiltration of the perivascular and intertubular connective tissue.

On the basis of experimental work De Gowin[6] and later Baker[1] have stated that renal insufficiency occurs only in the presence of an acid urine and that the administration of alkalies should prevent this complication.

Baker[1] states that no case of severe transfusion reaction has been reported where alkalies were given during the transfusion. Our patient received 15 gr. of sodium bicarbonate at the beginning of the transfusion and the first urine immediately after the reaction was alkaline. It is possible that a more serious reaction was prevented by giving alkalies in this case.

SUMMARY

1. A case of renal insufficiency is reported which occurred after transfusion of 1500 c.c. of citrated blood from the blood bank collected three days prior to the reaction. All three donors were later rechecked and their blood found compatible by typing and crossmatching.

2. Alkalies given prophylactically failed to prevent a severe transfusion reaction.

3. In our case and others reported hemolysis may occur without agglutination. Present methods of cross matching do not take this into account.

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DISCUSSION

DR. CHARLES A. GORDON.—Dr. Brainard has called our attention to a very important matter. To the obstetrician, more than anyone else, transfusion is of vital importance. Time is an important factor, yet proper cross-matching is essential. It seems however, that no matter how careful we may be, severe and unexpected reactions may occur.

In 1939, on the College Division at Kings County Hospital on the gynecological service alone, we gave 444 transfusions, and there were nearly as many on obstetric patients. We had three severe reactions, two in which cross matching was accurate and rechecked, and one in which the wrong blood was used. All our transfusions are from a blood bank.

Let us not get the idea that incompatibility of blood when cross matching has been properly done is common, for it is not.

THREE CASES OF CONGENITAL GOITER*

A. H. Parmelee, M.D., Edward Allen, M.D., Irving F. Stein, M.D., and Henry Buxbaum, M.D., Chicago, Ill.

THE occurrence of congenital goiter in this country is extremely rare if we are to judge from case reports in our medical literature. From the Chicago area there are no reports published in the last ten years. This is significant because this and the adjoining Great Lakes Region is considered goiter territory. In a recent article in a European medical journal, the statement is made that wherever goiter is endemic the incidence of congenital goiter constitutes an index of the severity of the endemic. If this is true, there can be very few places in America where goiter is endemic in any serious degree.

We are reporting three cases of congenital goiter not only because of the rare occurrence of the disease in this region, but also because in each instance the mother had been taking iodine throughout her pregnancy.

Case 1.—(Dr. Edward Allen.) Infant W., a white male, born at term May 16, 1939. The delivery was spontaneous after a four-hour labor. Birth weight was 6 pounds 6¾ ounces (2,900 Gm.). Color at birth was good, but cyanosis developed rapidly and he was resuscitated with difficulty. Severe dyspnea continued and breathing seemed possible only when the head was retracted. Oxygen was administered continuously. There was a large soft horseshoe-shaped tumor occupying the thyroid region, made up of three evenly rounded lobes. The left lobe was the size of a lemon, the right somewhat smaller and the isthmus was elongated and slightly nodular. The heart was enormously enlarged, occupying almost the entire left thoracic cavity, and a loud systolic murmur was heard over the precardium. All other physical findings were essentially negative. Dyspnea continued to be severe but by keeping him in a fixed position with the shoulders elevated so that the head dropped back, and by giving oxygen continuously, his color remained fairly good. The dyspnea and recurrent attacks of cyanosis continued but became gradually less severe. After eight days his respiration was quite normal. He was given breast milk by gavage for the first two weeks. Iodine ointment was applied as an inunction to the thyroid tumor from the second to the eighth day and again from the fifteenth to the twenty-third day. There was little change in the size of the tumor until after the sixth day when its size began noticeably to decrease. By the time of his discharge from the hospital it was only about one-third its original size. The size of the heart to percussion and also by x-ray examination had also decreased. Subsequently his condition has improved steadily and when last seen at the age of eight months he weighed 17¾ pounds and was normal in every way. The heart was normal in size and the thyroid gland was barely palpable. The skin and soft tissues of the neck were somewhat loose and redundant.

In Dr. Allen's history of the mother there are several significant facts. She was 27 years old. This infant was her second child. She had always been healthy except that during her first pregnancy she began to have asthma and during the last three months of that pregnancy took potassium iodide for relief. The first child was entirely normal, had no goiter, and weighed over 9 pounds. She continued to take potassium iodide frequently from July, 1937 until May, 1939 in large doses, not bothering to measure it with a spoon but drinking it directly from the bottle. She had no visible goiter when under Dr. Allen's care, but when she brought the baby to me eight months after she had discontinued the medication she had a mildly enlarged thyroid which she said she had noticed and that it was slowly increasing in size. She came to Chicago in November, 1938 from Texas and insisted she had never had any thyroid enlargement before.

*Presented at a meeting of the Chicago Gynecological Society, February 16, 1940.

CASE 2.—(Dr. Irving F. Stein.) Infant B., white female, born April 12, 1938, weighing 7¼ pounds (3,300 Gm.), after a twenty-three-hour labor, by low forceps delivery. The baby was in good condition and cried spontaneously, but the head was retracted and the respirations were labored. The thyroid gland was diffusely enlarged and all three lobes were palpable. Physical findings were otherwise negative. No active treatment was instituted and after six days the thyroid gland had decreased in size by 50 per cent. The baby was gaining well, seemed quite normal, and left the hospital with the mother on the tenth day, in good condition. When seventeen days old, the baby was given 1/20 gr. of thyroid extract, once daily and after three weeks of treatment the enlargement had almost entirely disappeared, only the isthmus being palpable. No enlargement whatever could be made out when the baby was four months old. The development since that time has been entirely normal.

This infant was the mother's second child. The first child was born four years previously and was normal. She was 29 years old. She was healthy and had no goiter. During both pregnancies she had been given Lugol's solution mm. x, t.i.d. from the second month to term because of tachycardia.

CASE 3.—(Dr. Henry Buxbaum.) Infant M., white male, weighing 6 pounds, 10 ounces (3,100 Gm.), born Feb. 28, 1935, after a nine-hour labor by low forceps delivery. The baby was deeply asphyxiated and resuscitated with some difficulty with a tracheal catheter. There was a large horseshoe-shaped tumor in the thyroid region, the right lobe was larger than the left. The physical findings were otherwise essentially negative. Aside from one short attack of cyanosis and some difficulty in nursing during the first few days, the infant's progress was normal. He was given no treatment and left the hospital with the mother at the end of ten days in good condition, weighing 6 pounds 8 ounces (3,000 Gm.). An x-ray examination on the second day after birth showed some compression of the trachea and a very large heart shadow which extended nearly to the left chest wall. The subsequent progress of the infant was good. The thyroid enlargement was still evident at three months though much smaller. At the age of one year the thyroid could no longer be palpated.

The mother was 32 years old, had been married fourteen years with no pregnancies until the present one. She had been healthy except that she had suffered from asthmatic attacks for the past ten years, and during the last five years had been taking large doses of potassium iodide continuously. In the fourth month of her pregnancy she had hyperemesis gravidarum from which she recovered under conservative management in the hospital.

COMMENT

Congenital goiter is very common in those parts of Europe where goiter is endemic. In certain parts of Switzerland, it was reported that one out of every two babies born had a congenital enlargement of the thyroid. In 1935 Ludwig Aschoff reported that, in Freiburg in Baden, 10 per cent of the neonatal deaths were due to congenital goiter. A goiter is present in the mother in a great majority of the previously reported cases: of the 53 cases reported by Demne, 23 had goiterous mothers; Richard's 43 cases had goiterous mothers in 23 instances. In Rübemann's 9 cases, Crattis' 7 cases, Räihäs' 11 cases, and Skinner's 14 cases, every mother had a goiter.

But not every mother who has a goiter will give birth to a child with a congenital goiter. In Räihäs' report of 11 cases, there were no instances of siblings that had had a congenital goiter. In each case, however, the mother's goiter had definitely increased in size during the pregnancy which resulted in a newborn infant with a goiter. He reported one remarkable case in which the patient was the mother's ninth child. During her previous pregnancies she had noticed no enlargement of her thyroid and had previous to that never had any semblance of a goiter. None of her other eight children had ever shown any goiter, then suddenly during her ninth pregnancy her thyroid began to enlarge and she gave birth to a child with a large congenital goiter. It would appear that in

this last pregnancy some endogenous or exogenous factor disturbed her endocrine glands, she developed a pathologic enlargement of the thyroid and simultaneously there developed a goiter in the fetus. The etiology of the goiter in the fetus seems closely bound up with the factor or factors that caused the goiterous enlargement of the mother's thyroid. It must also be admitted, of course, that many mothers develop a goiter during pregnancy and the infant born does not have a goiter.

The three theories advanced to explain congenital goiter are: (1) heredity, (2) infection, (3) iodine deficiency. Heredity can probaby not be ruled out, at least it would seem to be a contributing cause. Infection can probably be dismissed. As for iodine deficiency, there can no longer be any doubt of its enormous significance, whether or not it can be proved to be the primary cause. In Switzerland, where the use of iodized salt as prophylaxis is now obligatory, congenital goiter is rapidly becoming a rare clinical picture. Eggenberger now believes there is little support for the theory of heredity. A mother may have ever so large a goiter, but, if she takes iodized salt regularly during her pregnancy, she will never have a goiterous infant, he says.

Now, how are we going to explain the goiterous infants of these three mothers who all took iodine in large doses during their pregnancy? None of these three mothers had goiters but their newborn infants did. Aschoff says the etiology is closely bound up with the general metabolic condition of the mother. Hormonal disturbances of the mother may produce changes in the fetus which lead to thyroid enlargement. Thyrotropic hormones from the pituitary gland may be responsible. In our cases was the large amount of iodine ingested responsible for some profound metabolic disturbance, or endocrine imbalance?

Curtis and Puppel have shown that in exophthalmic goiter there is an increased mobilization and elimination of the body iodine, so that the patient may be in a negative iodine balance during certain stages of the disease even in the presence of a normally adequate intake of iodine. They further state that it is possible that the thyroid hyperplasia in hyperthyroidism is secondary to the increased loss of body iodine and is compensatory in an attempt to meet a continued bodily demand for utilizable iodine after the store of utilizable iodine has been depleted. "There is a striking similarity between the disturbed iodine metabolism in hyperthyroidism and the disturbed calcium metabolism of hyperparathyroidism." This similarity also extends to the disturbed sugar metabolism of diabetes.

Perhaps we may liken the hyperplasia of the fetal thyroid in these cases to the hyperplasia that occurs in islet tissue of the pancreas in the infants born of diabetic mothers. The etiologic significance, if any, of the iodine medication in these cases is still undetermined and we are anxious to have your suggestions.

55 WASHINGTON STREET

Arenas, N., and Echegaray, E. M.: Homolateral Hematometra and Hematosalpinx in a Case of Uterus Duplex, Rev. méd. latino-am. **25:** 297, 1939.

The authors review the literature of hematosalpinx and hematometra and present an interesting case of a 13-year-old girl in whom torsion of an ovarian cyst was suspected. She had suffered from increasing dysmenorrhea and abdominal colic since the menarche at the age of 12. At laparotomy, a left hematosalpinx was found and removed. The duplex uterus was noted each with its tube, round ligament, and ovary. Postoperative lipiodol study showed the right uterus to be permeable and revealed the presence of a right hydrosalpinx. The left uterus, which was atretic at the cervix, was removed at a second operation. The authors call attention to the importance of the symptom of dysmenorrhea, which is found in 95 per cent of cases of hematosalpinx, especially when accompanied by a palpable tumor in the tuboovarian region.

R. J. WEISSMAN.

AN ACUTE CRISIS OF SUPRARENAL INSUFFICIENCY COMPLICATING PREGNANCY*

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THE following case report is presented to call attention to the dangers incident to disturbance of the sodium-potassium balance in the blood serum.

Mrs. H. H. W., aged 32 years, a well-nourished white woman, first consulted Dr. Galloway on March 20, 1939. She presented apparently a normal three months' pregnancy. The past history was uneventful with the exception of a laparotomy for an ovarian cyst in 1930. After the operation she remained in the hospital for two months because of wound infection, a urinary fistula, and a thrombophlebitis of the left leg.

On March 20 her weight was 125 pounds; systolic blood pressure 120. The blood count and hemoglobin determinations were within normal limits. The physical examination revealed no important defects. Until the last of July the systolic blood pressure ranged from 110 to 130.

Throughout her pregnancy she complained of frequent "spells" of weakness and faintness. About the middle of June these became more frequent and severe.

On July 18 the urine showed two-plus albumin. Because of the albuminuria a 1,200 calorie salt-free diet was ordered. The weakness and albuminuria continued until July 28 when 2.5 Gm. of potassium chloride daily was ordered. On July 30 she complained of severe headache, severe abdominal pain, nausea, weakness, and vaginal bleeding. On July 31 she entered the hospital complaining of nausea, pain in the lower abdomen and back with a referred pain to the chest and shoulders, numbness in the arms and headache. She was in extreme shock with a thready pulse of 160, cold moist skin, and blood pressure of 96/70–. Her lips and finger nails were dusky. The physical examination did not reveal a cause for her condition.

She was treated for shock with elevation of the foot of the bed, heat, and adrenalin.

She temporarily improved but within an hour relapsed, her condition became alarming, the blood pressure was then 70/58. Following the intravenous administration of 1,000 c.c. of 5 per cent glucose in Ringer's solution, she improved and the blood pressure rose to 114/60.

Blood chemistry done on August 1 showed urea, 4.81 mg. per cent; uric acid, 2.5 mg. per cent; and chlorides, 494 mg. per cent. On August 2 the serum albumin was 3.88 per cent and globulin 1.77 per cent. Her condition remained the same with the blood pressure ranging from 110/60 to 95/60.

On August 5 she was seen by Dr. Sutton, when she had a pulse of 132 and a blood pressure of 95/60. An Ewald test meal revealed free hydrochloric acid 12 and total acidity 20, the basal metabolic rate was –4. The potassium chloride was discontinued and a full salt diet allowed, and an additional 2 Gm. of NaCl were given daily. The next seven days she remained weak, the pulse continued rapid, average 120, and the blood pressure varied from a systolic of 85 to 110. Beginning August 12 she was given 2 c.c. of suprarenal cortical extract daily and was allowed to leave the hospital August 18.

She remained at home until September 26 and continued on the same salt ration. A total of 10 c.c. of suprarenal cortical extract was given during the inter-

*Read at a meeting of the Chicago Gynecological Society, March 15, 1940.

val, nevertheless, she was practically bedridden, although the blood pressure maintained an average of 110/70. The albuminuria gradually disappeared.

September 26 she returned to the hospital to await her confinement. During the time preceding delivery she was in bed on a full diet to which 8 Gm. of NaCl was added daily. During this period she continued weak and complained a great deal of abdominal pain. The blood pressure continued above 105 mm. mercury.

After an uneventful labor she delivered a 3,370 Gm. female child. Immediately following labor she was given 1,000 c.c. of normal saline solution intravenously, and 2 c.c. of suprarenal cortical extract intramuscularly. A total of 8 c.c. of suprarenal cortical extract were given on both August 13 and 14, 6 c.c. on August 15 and 16, and 2 c.c. on August 17.

On October 18 she complained of extreme headache which was relieved only by ¼ gr. of morphine, hypodermically. At noon her blood pressure was 150/80 and 170/80 at 6 P.M.

On October 19 she received ¼ gr. of papaverine and on October 20 1 gr. was given at four-hour intervals for three doses and 1 gr. on October 21. The blood pressure gradually fell to 118/60 on October 22.

She returned home well, and on December 20 she had a blood pressure of 138/75. Her urine has shown no albumin. She feels well and is taking care of her apartment and baby without help.

This patient presents two interesting syndromes; namely, a typical Addisonian crisis followed later by an acute episode of hypertension.

The story of weakness and faintness followed by a crisis, the important symptoms of which were abdominal pain, nausea, collapse with extremely low blood pressure and rapid pulse, is readily ascribed to a crisis of Addison's disease. During the period preceding the onset of the crisis she was placed upon salt restrictions quite similar to that of a Wilder test for Addison's disease and in addition was given a total of possibly 6 Gm. of potassium daily. The estimate of potassium is based upon the assumption that the average diet contains 4 Gm. of potassium daily.

Although no pigmentation of the skin was found, the story of weakness, abdominal pain, and the reaction to a disturbance of the Na-K equilibrium, serve as evidence for the diagnosis of an insufficiency of the suprarenal cortex.

Subsequent events suggest that insufficiency of the suprarenal cortex was a temporary one during pregnancy. The cause of such an insufficiency is at best conjectural.

A logical assumption would be that as the result of the pregnancy the balance of the glands of internal secretion was disturbed.

The episode of hypertension can only be explained as an overactivity of the suprarenal glands with the cessation of pregnancy. The cortical extract used did not have a detectable quantity of epinephrin.

Even allowing that the diagnosis of suprarenal insufficiency is doubtful and the explanation of its cause more so, the case is still important, as it cells attention to the dangers incident to the disturbance of the Na-K equilibrium.

30 NORTH MICHIGAN AVENUE

Amolsch, Arthur L.: Congenital Atresia of the Tricuspid Valve Complicated by Congenital Myxosarcoma of the Labium Majus, Arch. Path. 24: 777, 1937.

Amolsch reports a case of primary congenital atresia of the tricuspid valve in an infant who died at the age of four months, bringing the total number of such reported cases to 45. The clinical symptoms were intermittent cyanosis, dyspnea, increased respiratory rate, and polycythemia. The clinical findings consisted of cardiac enlargement to the left, dilated right auricle, and a systolic murmur in the third intercostal space. The cardiac enlargement was borne out at autopsy. Another interesting finding was a congenital myxosarcoma of the left labium majus. This tumor was removed at the age of one month. Metastases to the lungs resulted.

WILLIAM B. SERBIN.

FILM SCALES FOR USE IN PELVIMETRIC ROENTGENOGRAPHY*

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In 1936 I presented in detail before the Radiological Society of North America,[1] some of the standard techniques of roentgenographic pelvimetry and commented rather freely upon the merits of each. Since then, I have encountered several hundred borderline pelves and have measured them by my simplified method of lateral roentgenography. It is the purpose of this paper once more to direct attention to the importance of x-ray pelvimetry and to present a modification in technique which yields many advantages.

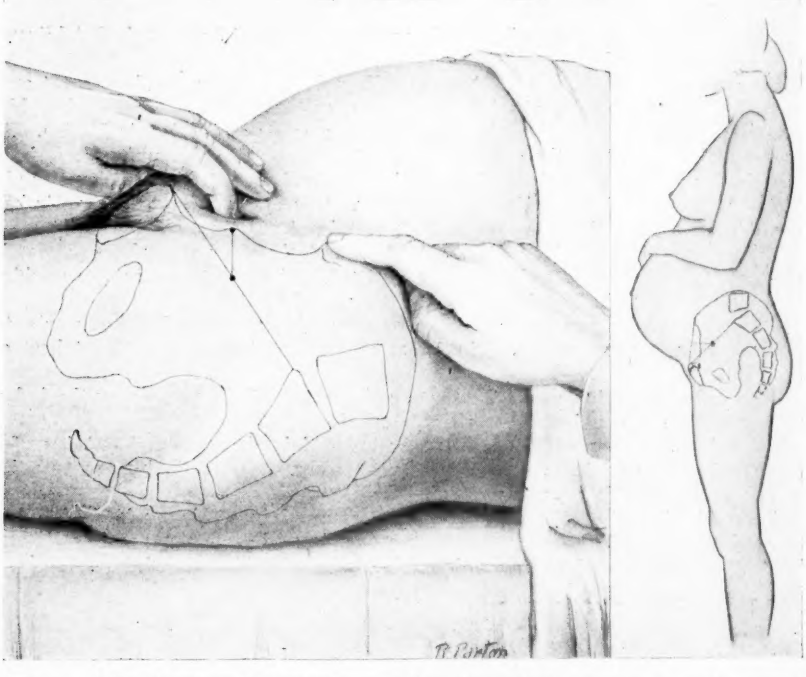

Fig. 1.—After locating the anterior superior iliac spine, pressure is made over the location of the anterior inferior iliac spine. The approximate middle of the true conjugate diameter lies one inch below this point when patient is in recumbent posture, or one inch posterior to it in standing posture.

One who has devoted much time to this phase of obstetrics is naturally gratified to note the increasing interest that is being shown by obstetricians and roentgenologists. Many more practitioners would utilize roentgenographic pelvimetry if they were familiar with a simple, reliable procedure. The fact that many methods are used and advocated increases confusion, since most men are unable to evaluate comparative advantages.

Distinction should be made between the two general types of x-ray pelvimetry; namely, (1) anteroposterior, and (2) lateral.

*Received for publication, Jan. 30, 1940.

My technique of anteroposterior roentgenography,[2, 3] although accurate, has the disadvantage of being rather technical and, for that reason, has not gained wide acceptance. The view of the inlet, obtained by anteroposterior roentgenography, possesses two features that are lacking in lateral roentgenography. These are the ability to measure the transverse diameter of the inlet, and to observe the contour of the pelvic brim.

The lateral technique, although lacking in these two respects, yields numerous other facts of importance, and is rapidly stimulating interest for the following reasons: (1) The procedure is inexpensive since it requires the use of only one film. (2) The method is very simple. (3) There is no inconvenience to the patient or doctor. (4) No elaborate apparatus is required. (5) The obstetrician or roentgenologist need not be especially skilled. (6) Important landmarks are readily distinguishable. (7) The topography of the pelvis is visualized and dis-

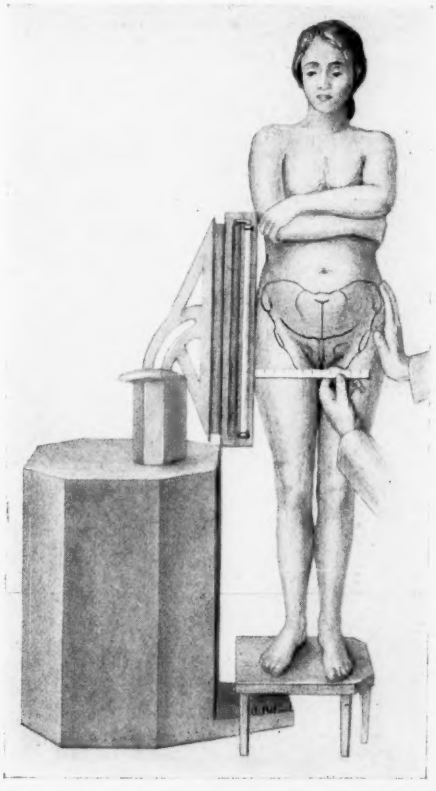

Fig. 2.—While making moderate pressure over patient's left hip, the distance from genital crease to surface of Bucky is measured. Since film is situated one inch behind this surface, one inch must be added, in order to obtain the true conjugate (inlet) -to-film distance.

crepancies from normal that may affect the mechanism of labor are easily discerned. (8) Pictures might readily be taken at term or even in labor, and accurate determinations arrived at. Such views permit not only mensuration of cephalic and pelvic diameters, but also permit a rather dependable interpretation of the relationship between the fetal skull and pelvic inlet. (9) Pelvic inclination may be noted. In this respect I shall subsequently direct attention to the usual method of engagement. (10) I know of no other method, regardless of complexity, that may yield more prognostic information than the simple technique here proposed, with the use of only one film.

A brief description of the procedure is warranted. With the patient in the recumbent posture, the doctor stands at her left side and places his right index finger upon her left anterior superior iliac spine, while the index finger of his left hand is passed downward along Poupart's ligament to the approximate location (distance of about two inches) of the left anterior inferior iliac spine. Pressure is made over this point. With the aid of a skin pencil, the station of this landmark (anterior inferior iliac spine) is lightly indicated on the lateral aspect of the patient's left hip. The approximate middle of the true conjugate diameter lies one inch below this point, and should be designated by a darker spot (one inch below light spot).

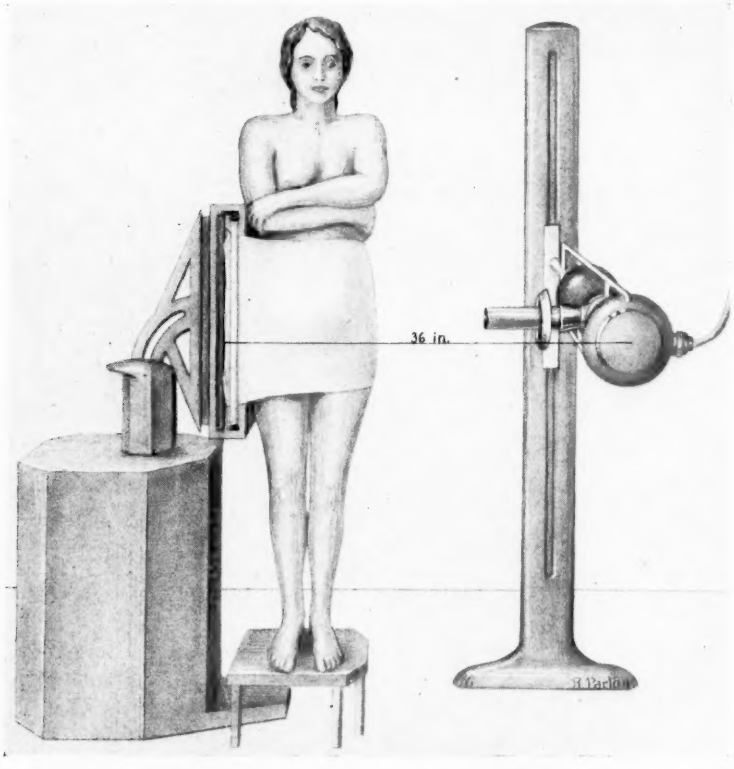

Fig. 3.—Patient secured in position and target of tube directed over the point denoting the approximate middle of true conjugate diameter.

Patient is now made to stand with right hip in contact with an adjustable vertical Bucky diaphragm. While applying moderate pressure to her left hip, the physician measures the distance from genital crease (plane of true conjugate diameter) to film, which is situated one inch behind the surface of the Bucky diaphragm. This is the "inlet-to-film" distance.

He then faces patient's left side, and sights her thighs, in order to have one hip directly over the other.

The target of the x-ray tube at a fixed distance of 36 inches from the film is directed over the dark spot on patient's left hip. Before exposure is made, patient is secured in position with the canvas binder that is routinely used by roentgenologists.

After extensive experience with the above procedure, I have found that the "inlet (genital crease)-to-film" distance varies from six to eight and one-half

inches in different women. So with the aid of the usual lead grid, having perforations 1 cm. apart throughout its surface, a series of film strips were prepared by placing the target of the tube 36 inches from a blank film, and interposing the lead grid 6 inches from the film, and taking a flash exposure. This film, after being developed, then becomes the 6 inch scale and may be used for computing measure-

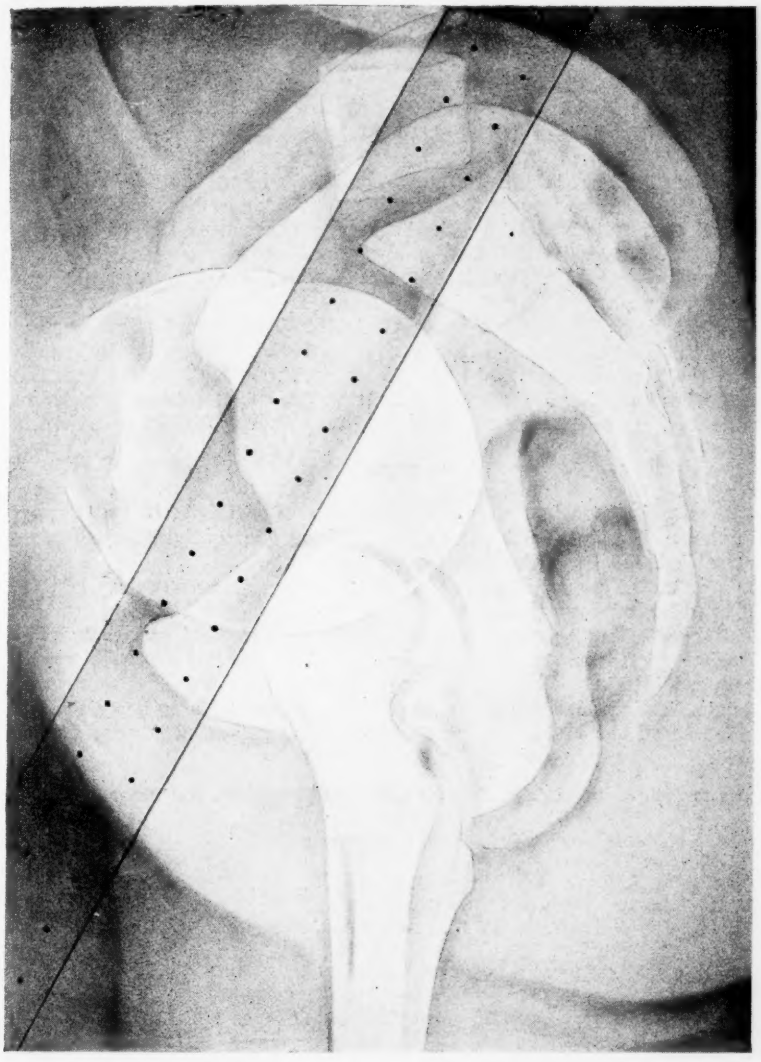

Fig. 4.—When the appropriate film scale is superimposed on the developed film, pelvic and cephalic diameters are readily measured.

ments on the film of any woman in whom the "inlet-to-film" distance is 6 inches. Similarly a film strip is prepared with the grid 6¼ inches from a film; another at a distance of 6½ inches; another at 6¾ inches and so on, up to 8½ inches, giving a set of eleven film scales. Each should be properly labeled.

The technique of pelvimetric roentgenography thus becomes simplified and less expensive, since all one need do is to take pictures at a fixed distance of 36 inches from target to film, and note the "inlet (genital crease)-to-film"

distance. After the film is developed and dry, the film strip that corresponds to the "inlet-to-film" distance is superimposed, and the true conjugate diameter measured by counting the dots between the middle of upper border of symphysis and sacral promontory. Using the same film strip, the presenting diameter of the fetal skull may be measured.

Much information to be gained from interpretation of the lateral pelvic roentgenogram has already been discussed.[4] I wish to direct attention here to the method of engagement of the fetal skull as viewed from the lateral aspect in the standing posture.

It is important to realize that when the pregnant woman stands, the presenting part of the fetus is more closely approximated to the pelvic brim. This permits of a fair comparison of the size of the fetal head and the true conjugate diameter. Disproportion is readily detected in many cases regardless of lineal determinations.

Also when the head is in contact with, or in, the brim, this pelvimetric technique yields reliable measurement of the presenting diameter of the fetal skull.

A head that falls away from the brim when the mother lies on her side has a tendency to enter or dip into the inlet when she stands.

In a remarkably high percentage of cases the biparietal enters the true conjugate diameter.

After working with Garnett[5] on pelvic inclination, my curiosity was aroused as to the method of engagement in cases of faulty inclination. It is surprising to observe that in the vast majority of such patients engagement occurs before term, the head making a right-angled turn on the spinal column in order to enter the inlet. This particular attitude on the part of the fetus is noteworthy.

CONCLUSION

A simple, inexpensive, accurate technique of pelvimetric roentgenography, which the author has found to be of unusual practical value in the management of several hundred borderline cases, is presented.

It is universally recognized that there actually exists an urgent need for the widespread use of x-ray pelvimetry.

Realizing that any procedure accepted for such general use, especially where the majority of men are not technically trained, must be one that will yield uniform readings in the hands of all practitioners, so as to afford a greater degree of standardization in prognostication of the patient with a borderline pelvis, I have presented the technique described with the hope that it may be generally adopted.

Film scales are manufactured and sold by Bastion Bros., Rochester, N. Y.

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(1) *Jacobs, J. Bay:* Radiology **28**: 406, 1937. (2) *Idem:* South. M. J. **25**: 828, 1932. (3) *Idem:* Am. J. Obst. & Gynec. **32**: 76, 1936. (4) *Idem:* Ibid. **28**: 227, 1934. (5) *Garnett, A. Y. P., and Jacobs, J. Bay:* Ibid. **31**: 388, 1936.

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SUCCESSIVE, COEXISTENT TUBAL PREGNANCIES*

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MULTIPLE pregnancies, at least one of which is tubal, are rare enough to be a medical curiosity. Bilateral tubal impregnation is still less frequent, and according to Fishback only 76 such cases have been reported in the literature (1939). Our case and one reported by Torpin in a recent issue of this JOURNAL makes a total of 78 cases. This finding, seldom recognized before operation, is of some practical importance in that it illustrates the necessity of inspecting both adnexa at the time of operation.

On Jan. 19, 1938, at 7:00 A.M., an unmarried white woman (E. E.), aged 25, on awaking, noted generalized lower abdominal pain, more severe on the right side and radiating to the back. She felt weak, vomited, and had a fruitless desire to defecate. At 9:00 A.M. one of us (W. J. H.) found her in shock, with a rigid abdomen, and the classical symptoms of severe intra-abdominal hemorrhage. Her blood pressure was 60/40, pulse 140, temperature 97° F., and respirations 40. Both pupils were dilated. There was exquisite tenderness over the entire abdomen, more marked on the right side. Shifting dullness in both flanks and a bulging cul-de-sac were noted. On rectal examination a tender mass 3 cm. in diameter was felt in the midline behind the uterus.

At 9:30 A.M. she was admitted to the Bryn Mawr Hospital by ambulance and was immediately prepared and examined vaginally. A diagnosis of ruptured left tubal pregnancy with severe intra-abdominal hemorrhage was made. She was immediately taken to the operating room and a lower abdominal midline incision was made, while transfusion from a supply of banked blood was begun.

The peritoneal cavity was full of blood. The left adnexa were delivered and the mass which had been palpated preoperatively was inspected. It had the typical gross appearance of an unruptured tubal pregnancy. Since there was no bleeding in this situation, the condition of the opposite tube was immediately investigated. The distal one-third of the right tube opposite its mesosalpinx was ruptured for a distanec of 3 cm. An effort at clotting had taken place and in the partially formed clot a fetus (5 cm. in length) was lying. The shattered tube was removed in the routine manner and the left tube excised immediately afterward. The round ligaments were quickly shortened and the abdomen closed in layers while the blood transfusion was completed. After an uneventful convalescence and primary union of the incision, the patient was discharged from the hospital on Feb. 2, 1938.

The following is the pathologic description of the tissue removed: The walls of the ruptured right tube were distended, thickened, and infiltrated with chorionic villi and blood. Section showed hyperplasia of the muscular elements, with edema and lymphocytic infiltration. Part of the mucosa was replaced by decidual tissue; in other parts it was hyperplastic. The fetus was 5 cm. long and microscopic examination showed it in a state of good preservation.

The left tube was dilated in its middle portion and contained an organized clot 15 mm. in diameter. Microscopic examination showed moderate hyperplasia of the mucosa of the tube. The contents, consisting of clotted blood, showed areas of necrosis, fibrous tissue interspersed among fairly well-preserved placental tissue and decidua, with infiltration of polymorphonuclear leucocytes.

After the convalescence had progressed satisfactorily, the following information, previously unknown, was obtained from the patient. Her past medical history was irrelevant, in no way suggestive of previous pelvic disease. The last

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

normal period occurred Nov. 25 to 29, 1937. On December 20 she had what she regarded a normal period except that its duration was seven days. After an interval of two days, bleeding recurred for another seven-day period. Following this there was daily spotting of reddish brown blood until the onset of the present illness. Two weeks before admission the patient had an attack of nausea, vomiting, and moderate pain in the right lower abdomen which she did not consider serious enough to mention to her physician who treated her at that time for an upper respiratory infection. It was impossible to learn any facts which enabled us to estimate the duration of the pregnancy on the opposite side or to determine when impregnation had occurred. This experience is similar to that related in most of the other reports regarding this unusual condition.

The title of this paper is not meant to imply that the two pregnancies were viable simultaneously but that impregnation must have occurred in each tube within a comparatively short interval of time. The title is intended to convey the fact that impregnation occurred in the right tube before the pregnancy in the left tube had undergone complete resolution.

REMOVAL OF A GRÄFENBURG RING WITHOUT INTERRUPTION OF PREGNANCY*

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THE Gräfenburg ring is a closely coiled spiral of fine silver or gold wire curved to form a ring 1.5 to 3 cm. in diameter. When placed within the uterine cavity this device decreases fertility. It is not a contraceptive, because it does not prevent, although it may interfere with union of the sperm and ovum. It is a means of birth control, because it may prevent nidation of the fertilized ovum, or it may act as an abortifacient if nidation does occur. The Gräfenburg ring has been used extensively abroad, less frequently in this country. It is an unsatisfactory instrument because it does not prevent intra- or extrauterine pregnancy, it predisposes to pelvic infection, it may perforate the uterus, and it may be lost without the patient's knowledge. For these reasons, based upon dozens of unfavorable reports, the use of an intrauterine foreign body (Gräfenburg ring, gold stem pessary, Pust star, etc.) as a "contraceptive," is regarded as dangerous practice if not malpractice.

The following report is made because no similar case was discovered in a review of some 50 publications on the Gräfenburg ring.

Mrs. A. S., aged 33, gravida iii, para i, reported for prenatal care on Nov. 4, 1938, eight weeks after her last menstrual period. She was married in 1929, was delivered spontaneously of a normal infant in 1930, and in 1931 consulted Dr. Ernst von Gräfenburg for contraceptive advice. He fitted her with an intrauterine silver ring. Each year thereafter he saw the patient and removed the ring for a period of four weeks. During the rest of the year the ring was worn continuously. He used three different rings. The first, of silver, was removed because of abdominal pain. The second ring, of gold, "slipped" and was replaced on March 5, 1935 by a larger coiled gold ring which was worn continuously until November, 1938. The patient considered the Gräfenburg ring an ideal contraceptive although 2 pregnancies had occurred, one ending by miscarriage at the eighth week and the present one.

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 7, 1940.

The last menstrual period (Sept. 10, 1938) was followed by mild lower abdominal pain and slight spotting on October 10. No other symptoms developed. Pelvic examination on November 4 showed a two months' pregnant uterus. The Gräfenburg ring could be palpated through the anterior uterine wall at the level of the internal os. X-rays showed the ring clearly. The patient was admitted to the hospital, and, under nitrous oxide anesthesia, the cervix was gently dilated, the ring grasped with hemostats and removed (Fig. 1). Large doses of pantopon

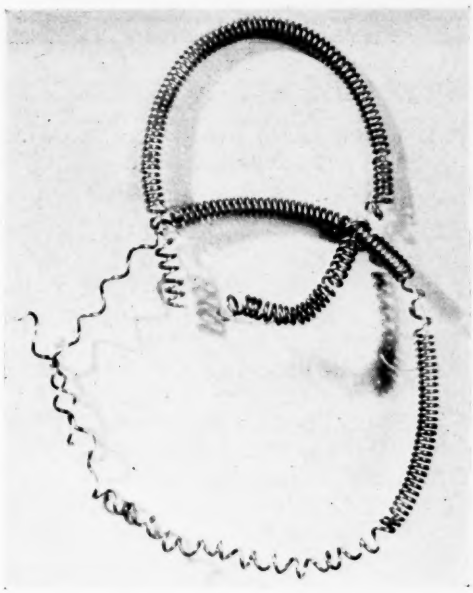

Fig. 1.

were given, and, after four uneventful days, the patient was discharged from the hospital. The remainder of her pregnancy was uncomplicated, and she delivered a healthy eight-pound baby spontaneously on June 5, 1939. The puerperium was afebrile and uneventful; mother and baby were in good health at last report (February, 1940).

807 Spruce Street

Vignes, H.: The Nicolas-Favre Disease in Gynecology and Obstetrics, Rev. franç. de gynéc. et d'obst. **34:** 215, 1939.

The pathogenic agent responsible for the Nicolas-Favre disease is a specific filtrable virus which is lymphotropic. The patient exhibits a chronic vulvar ulceration with hypertrophy or perigenital masses with or without a rectal stricture or an obstruction during labor. The cases with vulvar manifestations are usually seen in clinics for venereal diseases. Because of the marked induration, these lesions produce formidable obstructions to normal delivery. In some cases these lesions are associated with inexplicable peritonitis.

Vignes emphasizes the strikingly large number of fetal deaths in these patients. He mentions a case reported in the literature where not only the mother but also the baby soon after birth had a positive Frei test.

J. P. Greenhill.

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

RADIUM THERAPY IN GYNECOLOGY

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THE radiologist has invaded many fields in gynecology which, formerly, were largely amenable to surgery only, so that today radium and x-ray are firmly established as essentials in the gynecologic armamentarium. Consequently, it is obligatory for the gynecologist to be familiar with the use of these modalities.

This discussion will be confined to the use of radium in gynecology and will refer only to x-ray therapy as an adjunct. Radium is used in gynecology to treat benign and malignant neoplasms and certain functional disorders. In order to employ radium safely and efficiently, its effect upon normal and malignant tissues must be understood, and the dangers and possible complications resulting from its use must be fully appreciated. This implies a knowledge of the dosage and screening necessary to accomplish the result desired.

It is the effect of the gamma rays, given off by the radium element, which is of therapeutic value. The beta rays, or burning rays, are harmful and must be eliminated by proper screening. The alpha rays are weak and are of no significance. Radium does not remove a cancerous growth by destruction of the entire part affected, as is accomplished by surgery or cauterization, but the gamma rays have a direct selective action on the cancer cells, destroying them without injuring the normal cells at the site of the neoplasm. This is demonstrated in healed cases of carcinoma of the cervix, where the normal shape of that organ may be restored without trace of the site of the growth.

Another action of radium is to cause proliferation of the connective tissue. The connective tissue contracts, with resultant obliteration in a great degree of the blood and lymph supply, producing the contracted, pale-looking cervix and funnel-shaped vaginal vault noted in ideally healed cases.

If the dosage suitable for a certain case is used, the cancer cells, but *not* the normal tissues, will be destroyed, owing to the selective action of the gamma rays on the carcinoma, and the greater resistance or toleration of the normal tissues. If much larger doses of radium than is required to destroy the cancer cells are given, the normal structures will also be destroyed, thus producing extensive necrosis with its resulting septic absorption, hemorrhages, and injury of adjacent viscera, with, perhaps, the production of fistulas. These unfortunate results of overradiation with this powerful element are commonly attributed to the extension of the carcinoma, or, frequently, the action of the radium is blamed and, consequently, condemned as of no value. We must also

remember that if too small an amount of radium is used, or for too short a time, we may fail to destroy all the cancerous tissue.

The elimination of the beta, or burning, rays, which cause extensive destruction of the normal tissue, depends upon the proper screening of the radium. Various metal containers of different thickness are used for this purpose, such as platinum, gold, silver, or brass, and damage of the bladder and rectum is avoided by "distance screening," that is, pushing them out of reach of the rays by overdistending the vagina with gauze. If inadequate screening has been used, unnecessary necrosis will result.

Too frequently repeated radiations, especially if a heavy dosage for prolonged periods is employed, will result in the so-called "late reaction" of radium. Six months, or a year or more following the initial treatment, dense infiltration, pelvic pain, ulceration, and discharge may develop, which is likely to be attributed to a *recurrence* of the disease, when it is actually the result of an overirradiation of the tissues, with a resulting excess of connective tissue formation. This produces a slowly developing obliterative arteritis, and the devitalized structures ulcerate and become a ready prey to infection.

Radium also has an action on the ovaries, the follicular apparatus being very sensitive to the rays, so that it may be destroyed, with a resulting atrophy of the organ, inducing the menopause, as in castration. This action of radium may be used to control excessive uterine bleeding by retarding the ovarian function. It also has a local action in the endometrium, causing destruction of the glandular elements, with replacement of connective tissue. The castration effect on the ovaries naturally results in atrophic changes, to which may be attributed the shrinking, or even disappearance, of myomas. The element, either in the form of a salt or the emanation, may be used with equal results. Our work at the Woman's Hospital in New York has been done entirely with the salt in the form of radium barium sulphate.

Large quantities of radium are not advantageous for internal application. The curative penetration of the gamma rays, in amounts which may be safely used, is limited to about 3.5 cm. Necrosis of the tissues may be caused at the site of application by the gamma rays breaking up into secondary rays from the metallic screens and their action on striking the tissues. An attempt to limit the action of these secondary rays is made by using aluminum or pure rubber protection. It is of no avail to attempt to secure a deeper penetration in an effort to reach the parametrium by greatly increasing the amount of radium in the container, because the intensity of radiation is decreased inversely in proportion to the square of the distance, and the result would be a marked and unnecessary increase of the local damage without appreciable gain in penetration.

FREQUENCY AND ETIOLOGY OF BLEEDING

In the past ten years, 19,603 gynecologic patients were discharged from the Woman's Hospital in New York. Severe hemorrhage, as a predominant symptom, occurred in 371 cases, or nearly 2 per cent. It was present in 254 tubal pregnancies, as a complication in 4 cases of carcinoma of the fundus of the uterus, and in 53 cases of carcinoma of the cervix. Secondary hemorrhage as a postoperative complication occurred in 26 cases of amputation of the cervix, in 23 cases of cauterization or conization of the cervix, in 1 case of plastic operation on the

pelvic floor, and in 8 cases of plastic operation on the vaginal walls. There were 2 cases of hemorrhage in which the cause was undetermined.

Weintraub of Brooklyn, in a recent report, found the frequency of uterine hemorrhage in 4,421 gynecologic cases other than pregnancy, to be 738 or 16.6 per cent. The most common single cause was fibromyomas, in 46 per cent. Endometrial hyperplasia occurred in 23.7 per cent, usually associated with follicular cysts of the ovary; 9.2 per cent were due to fibrosis uteri, 6.6 per cent to cervical or fundal polyps, and to malignancy in 3.7 per cent.

Floyd Keene, of Philadelphia, studied 782 cases of postmenopausal bleeding and found 60 per cent were due to malignancy; 78.4 per cent were associated with some form of neoplastic disease of the cervix, fundus, or adnexa, and 75.4 per cent of these were malignant. In the entire series, bleeding was of cervical origin in over one-half of the cases, and 56 per cent of these lesions were malignant; 40 per cent were fundal in origin, of which 61.5 per cent were malignant. In 38 cases no organic lesion could be found.

Howard Taylor, Jr., of New York, in a study of 406 cases of postmenopausal bleeding, and TeLinde of Johns Hopkins Hospital, in a study of 349 cases, found approximate percentages.

Postmenopausal bleeding, especially after a year, therefore, is always important, as, with a normal cervix, two-thirds of the cases are of malignant origin.

FUNCTIONAL HEMORRHAGE

Uterine hemorrhage may be regarded as functional only when no general or local lesion can be found, the bleeding symptoms in all being similar. Functional bleeding may occur during adolescence, the reproductive period, at the menopause, and later. The accepted theory is that it is due to a disturbance in the ovarian rhythm.

As the cyclic phase of the endometrium reflects the ovarian activity, a biopsy of the endometrium is essential as an index of the ovarian function in all cases of functional bleeding, and the most common finding is that of hyperplasia, frequently of the polypoid or Swiss cheese type.

The thyroid gland is an important factor in adolescence. Hyperthyroidism or hypothyroidism may be a factor in irregular bleeding, and the basal metabolic rate should be ascertained and the appropriate therapy employed.

Fatal functional bleeding has occurred in adolescence.

In functional bleeding in women of the childbearing age where hormone therapy has failed, curettage and intrauterine application of radium of from 300 to 400 mg. hours is indicated. We have found that 600 mg. hours is within the danger zone of castration.

Norris and Behney of Philadelphia, in 1,437 cases of benign hemorrhage, found that 750 cases were functional and 687 were myomas. Satisfactory results were obtained in 83 per cent by the use of intrauterine radium therapy; 3 per cent developed relapses ten years or more later. Carcinoma developed after irradiation in 1.09 per cent.

In functional bleeding at or after the menopause, the most satisfactory treatment is a diagnostic curettage to rule out possible malignant disease, and the intrauterine application of radium, 1,800 mg. hours being an average dosage to insure permanent stoppage of the bleeding. We believe this is preferable to ovarian radiation by the x-ray. Transfusion should be used in patients with a low hemoglobin.

If, in postmenopausal bleeding, with a slightly enlarged uterus and ovary, the biopsy reveals a hyperplasia of the endometrium, a granulosal cell tumor should be suspected.

NONMALIGNANT DISEASES

The benign conditions which may be treated by radium therapy are derangements of the physiology of the uterus, as a result of ovarian or pituitary dysfunction, or the menopause, and the symptoms produced by benign neoplasms. The outstanding objective symptoms of these benign or malignant conditions are uterine bleeding, either in excess at the menstrual period, or in irregular and too frequent periods, "spotting" or in prolongation of the menopause. It will be of value, therefore, to consider uterine hemorrhages in this connection.

Uterine bleeding, other than the normal physiologic loss of blood during menstruation, is probably one of the most frequent conditions that the general practitioner, as well as the gynecologist, has to contend with, and a correct diagnosis as to the cause may be of vital importance as to whether it is of benign or malignant origin.

The causes of nonmalignant hemorrhages may be classified as follows:

1. Functional hemorrhages, as a result of endocrine dysfunction and imbalance, occurring at puberty, during the childbearing period, and at the menopause where there is no demonstrable lesion.

2. Hemorrhages associated with neoplastic diseases, including cervical and corporeal polyps, myomas, adenomyosis, and ovarian tumors.

3. Hemorrhages associated with inflammatory diseases, as salpingitis, oophoritis, and tuberculosis.

4. Bleeding from retained gestational products after abortion or full-term delivery.

5. Intra-abdominal hemorrhage, as a result of ectopic pregnancy, endometriosis and ruptured ovarian cysts and myomas.

6. Uterine bleeding from miscellaneous causes, such as cervicitis with erosion, subinvolution, hemophilia, hypertension, and postoperative hemorrhage.

NEOPLASTIC DISEASES

Cervical and fundal submucous polyps are prone to hemorrhage of a continuous "spotting" type, especially after coitus, douche or exercise, with menorrhagia at the menstrual period, and there is usually a polypoid type of endometrial hyperplasia present. The treatment is surgical.

Cervical or fundal submucous myomas are prone to severe and dangerous bleeding, probably as a result of necrosis and ulceration. It is the consensus of opinion that myomas which do not invade or encroach upon the endometrium are not the cause of uterine bleeding. There is a prevalent conception that abnormal bleeding is a specific characteristic of fibroids entirely distinct from hemorrhage from nonmyomatous uteri. As Graves of Boston has emphasized, the processes that lead to bleeding are hormonal and not dependent on the myomatous growth itself. The bleeding, then, in nonmyomatous and myomatous uteri is identical in origin, that is, hormonal.

There is no bleeding or change in the endometrium in fibroid uteri unless there are cystic changes and absence or defect in the corpus luteum of the ovaries, the exception to the above being in the submucous myomas. In such cases there is an abnormal vascularity of the growth, and the area of the uterine cavity is increased. The contractions of the

uterus and the corrosive action of the menstrual ferment trypsin, all favor rupture of the delicate superficial vessels on the surface of the submucous growth, and necrosis or trauma causes rupture, with resulting menorrhagia or metrorrhagia with clots. This is always of a venous type and may be controlled by packing. Bleeding from a fibroid uterus after the menopause is always to be considered of importance. It may be from a necrotic submucous growth, sarcoma or carcinoma.

Surgery is indicated in bleeding myomatous uteri, as a general rule. Myomectomy in the childbearing age, with removal of a submucous growth by vaginal hysterotomy, may be possible. If the myomatous invasion of the uterine musculature is too extensive, hysterectomy is indicated with conservation of the ovaries in young women.

Radiation is not suitable in the third or fourth decades for bleeding in the presence of myomas, as a sterilizing dose is necessary to produce the desired result. An inadequate nonsterilizing dose will give temporary relief of the bleeding, but the myomas will develop further. Radiation is excellent in the fifth decade for abnormal bleeding with associated small intramural growths. A sterilizing dose must be given so as to destroy the function of the ovaries. Radium is preferable to x-ray therapy in my experience in such cases. Radium is of no use in the treatment of postclimacteric fibroids without bleeding. If the growths produce pressure symptoms, hysterectomy is necessary.

Adenomyosis is a nonneoplastic disease, but is due to an invasion of endometrial glands into the uterine muscle tissue with resulting hypertrophy. Sampson's theory of endometriosis may account for the invasion of the musculature of gland elements. Abnormal bleeding is the most important symptom, usually with a profuse menorrhagia and a symmetrically enlarged uterus without intermenstrual flow. Radiation therapy is of little benefit in this type of disease, and its failure to relieve the bleeding may be of diagnostic value. Surgery is indicated.

Generally speaking, benign ovarian neoplasms do not cause bleeding, and until their size is demonstrable or complications set in, they are frequently not discovered. Cystic degeneration of the ovaries may develop prolonged menstruation or "spotting" due to the imperfect formation of the corpus luteum, especially if there is formation of a corpus luteum cyst. Simple follicular cysts frequently cause no menstrual irregularity. Menstrual disorders are noted in about only 12 per cent of dermoid cysts and pseudomucinous cystadenomas. The granulosal cell type of tumor, however, is frequently associated with bleeding.

These ovarian neoplasms are all best treated by surgery and not by radiation therapy. In patients beyond 40 years of age with fibroid uteri, radium therapy may be employed successfully only where the physical and symptomatic conditions present are suitable. Each case must be given individual consideration.

It is well to remember that 28 per cent of all women over thirty-five years of age have fibroids in some degree, and many are without symptoms throughout life. These cases should, of course, be watched, but without symptoms treatment may not be essential. When bleeding occurs as a symptom, about one-third may be treated successfully with radium. The limitations, however, are definite. Radium is not suitable for women who desire the preservation of the menstrual function and possible future pregnancy.

Indications and contraindications for radium therapy in uterine fibroids:

The size of the growth must not be over that of a three or three and one-half months' gestation.

The growth must be fairly symmetrical or globular in shape.

The most suitable cases are those with intramural fibroids.

Subperitoneal or pedunculated growths outside the range of the rays are not influenced by the radium.

Submucous fibroids are a contraindication to radium on account of the danger of infection. Rapidly growing growths suggest sarcoma or progressing degenerative changes and are not suitable.

It is essential that the adnexa be entirely free from pathology.

Fibroids showing degenerative changes, as indicated by infection (temperature and tenderness), or anemia out of proportion to the blood loss, are not suitable for radium therapy.

TECHNIQUE OF APPLICATION

It is our opinion that anesthesia in some form should be employed in all cases in which radium is employed. This not only prevents suffering, but allows a thorough examination and exposure to insure a correct diagnosis, enables the operator to make an accurate application and fixation of the element in the situation desired, and to place adequate screening for the protection of the adjacent organs. Likewise, a diagnostic curettage should always be done at the time of the application in all suspicious benign cases, as not infrequently an adenocarcinoma of the fundus may be discovered which will, of course, alter the conduct of the case. Gas-oxygen anesthesia is sufficient, and in many cases a half dosage of spinal anesthesia is very satisfactory.

In the treatment of fibroids the radium should be so distributed in the container, as to contact as much of the endometrium of the corpus uteri as is possible, covering the area from fundus to internal os.

It is most important that the container should be anchored in its position, as the natural contractions of the uterus to expel a foreign body are often the cause of an unsatisfactory result or a radium burn of the vagina.

It is our custom to always test the presence of the radium in the applicator with an electroscope at the time of the insertion. This is a wise precaution.

The amount of radium element used in the treatment of fibroids is usually two tubes of 50 mg. each, placed in tandem formation in a container giving an equivalent of a milligram of platinum screening, with a pure rubber or aluminum outer filter to eliminate the secondary rays. The dosage for myomas averages from 1,200 to 2,400 mg. hours, depending upon the size of the uterus and the thickness of the uterine walls.

Great importance is attached to the insurance of the maximum of distance screening by distending the balloon-shaped vagina to the utmost with firm gauze packing, in order to displace the adjacent bladder and rectum as far away as possible from the effect of the rays. This naturally interferes with the patient's ability to void, so it is well to insert an indwelling Pezzer catheter, not only to avoid repeated and sometimes difficult catheterizations, but also to keep the bladder collapsed, and the posterior bladder wall is thus kept away from the danger zone of radiation through the anterior uterine fundus. One application only is best in these cases. The hemorrhage will be checked

promptly; perhaps one subsequent period may occur. The growth will show a gradual shrinkage during a period of ten to twelve months.

Radium should only be used in women under 40 years of age, when serious systemic disease contraindicates a major surgical procedure.

In myopathic bleeding at the menopause, with frequent excess and prolongation of that period, permanent sterilization with radium is an ideal and simple procedure. It should always be preceded with a diagnostic curettage at the time of the application. The radium should be applied in tandem to the corpus, and the usual dosage is from 1,200 to 1,800 mg. hours, depending upon the size and thickness of the uterus.

In myopathic bleeding in the childbearing age, temporary sterilization with radium may be employed. From 300 to 400 mg. hours is the usual dosage which may result in a temporary amenorrhea for several months. A second application may be required later, but in my experience 600 mg. hours is near the danger zone of permanent sterilization.

In severe intractable cases of dysmenorrhea in young girls, temporary sterilization may be of some avail, but permanent sterilization is unwise because of the menopausal changes and symptoms which will ensue. Hysterectomy, with conservation of the ovaries, would be a much more satisfactory and justifiable procedure.

In endometriosis, a permanent sterilization would be necessary to effect a cure in most cases, and as this usually occurs in young women, surgery would be the method of choice, as some conservation of ovarian tissue may be possible.

Temporary sterilization with radium, however, will relieve symptoms in some cases with involvement of the rectovaginal septum. Temporary sterilization with radium in the childbearing age, according to Douglas Murphy and others, may possibly lead to developmental defects in subsequent offspring, appearing in the third or later generations.

Without doubt radiation *after* fertilization of the ovum in the earlier months of pregnancy will produce marked defects in the progeny. Therefore, radiation should never be done in the presence of pregnancy, except in cases of carcinoma.

MALIGNANT DISEASES

While cancer is a disease that attacks all parts of the body, about 25 per cent of female deaths from cancer are due to carcinoma of the uterus, and the average duration of life is about twenty to twenty-four months without treatment.

As cancer of the uterus is a type of the disease which every general practitioner encounters in his practice, it is largely to him that we must look for the early recognition of the disease and the education of his patients to the importance of promptly seeking a diagnosis on the appearance of suspicious symptoms.

We must appreciate that the disease originating in the cervix and that arising in the fundus must be considered separately, as the clinical course and the results of treatment are quite different in each instance.

CANCER OF THE CERVIX

Cancer of the cervix, by reason of the anatomic conditions, is by far the most dangerous form and the most difficult to cure, and is also the most frequent. At the outset we must admit that the results of the treatment of cancer of the cervix are far from satisfactory, but, at the

same time, we must appreciate that there has been a considerable gain in the percentages of cures and palliations as a result of modern methods. We have a choice of treatment in the operable cases of surgery or radiotherapy, but if we use surgery we must employ the radical Wertheim technique.

The difference between the ordinary panhysterectomy and the Wertheim operation may be best appreciated when likened to a simple mastectomy, as compared to the modern radical removal of the breast with the pectoralis muscles, and the thorough cleaning out of the axilla of the lymphatic glands. A simple mastectomy for cancer of the breast would not be considered justifiable from the surgical standpoint today, yet it is known that many women with cancer of the cervix are being subjected to an ordinary hysterectomy instead of the radical operation, due to the fact that the average general surgeon is not competent, owing to the lack of experience and failure to develop the necessary skill, or he fails to appreciate what the technique of the radical operation should be.

One of the outstanding surgeons in this particular field today is Victor Bonney of London, and I would commend his Hunterian Lecture on the "Surgical Treatment of Carcinoma of the Cervix" to those who wish to obtain a proper appreciation of the technique and the difficulties of this formidable operation.

There is no difference of opinion as to what is the best treatment at our disposal for the inoperable class. Radiotherapy is admittedly our most valuable palliative measure, definitely prolonging life and, in a small percentage of cases, approximately 12 per cent, accomplishing a cure.

Today, owing to the technical difficulties and the prolonged hospitalization and suffering, and to the high primary mortality rate, 8 to 17 per cent, with no gain in so-called cures, surgery has largely been replaced by radiation therapy in cancer of the cervix, with its primary mortality of less than 2 per cent, and an even greater salvage.

The technique of the application of the radium in these cases seems so simple that it is difficult to impress upon the casual observer that success and safety depends upon the careful study of the location and extent of the disease, of the type of cell and the degree of its maturity, of the general physical state of the patient as to age, blood condition and toxemia, of the careful preoperative preparation of the patient, of the amount of radium used and its distribution in appropriate containers, on the proper employment of screening to cut out the burning rays, on the placing and maintaining of the radium in situ where it will destroy the cancer and yet not damage adjacent viscera, on the duration of the application, and the time and dosage of reradiations and deep x-ray therapy, and, finally, on a careful frequent follow-up. A personal experience in studying the action of radium on this disease over considerable periods of time is essential before one can become competent to treat properly cancer of the uterus with radiotherapy.

This statement may be made in spite of the assurances given the practitioner in the alluring advertisements in the medical press, that it is so simple that all he has to do is to send a description of the case and the radium with full directions will be forwarded. Correspondence courses in radiotherapy are dangerous, and I wish to sound a warning as to the serious harm that may result from the indiscriminate application of radium by inexperienced hands. I have seen a number of instances of grave permanent damage through the careless and ignorant

use of radium by those not qualified. The renting of radium from commercial agencies is, of course, perfectly justifiable, but the knowledge and judgment as to how and when to use it can only be accomplished by careful study and personal experience and observation in radiologic clinics. I cannot do better than to quote Regaud's recent warning: "It is necessary to have much experience to obtain from this method of treatment all the good that it may give without the evil that it may do."

Two main histologic types of cervical carcinoma are recognized—the epidermoid carcinoma and the adenocarcinoma. The epidermoid carcinoma, which is much the most frequent, is divided into three classes, according to the differentiation of the type of cell. The epidermoid group is the most common form, and the cell types are designated as the squamous or spinal cell, which is the most mature or "ripe" cell, the transitional or plexiform "midripe" cell, and the anaplastic spindle, "unripe" cell.

The adenocarcinoma is chiefly recognized by its glandular form of growth.

The importance of recognizing these various types of cancer cells will be appreciated when we understand that they respond differently to irradiation. The "Law of Bergonie and Tribondeau" states that "Immature cells and cells in an active state of division are more sensitive to irradiation than are cells which have acquired their fixed adult morphologic and physiologic character." The squamous spinal, or mature, cell is much the more radioresistant and, at the same time, it is more slowly growing and the least malignant type, while the embryonic anaplastic "unripe" spindle cell is the least radioresistant, but the most rapidly growing and most malignant type. The transitional or "midripe" cell is midway between these two extremes in responding to irradiation. Adenocarcinoma of the cervix is, fortunately, much less frequent (our ratio is about 13 to 1), as it is very radioresistant and more difficult to cure.

The ability to make a prognosis as to the probability of obtaining a cure by studying the type of cell is open to debate and is not uniformly accepted, as it is evident that many other factors must be taken into consideration, notably the extent of the disease and the physical resistance of the patient; also that the ordinary biopsy does not permit a study of the complete specimen which may show considerable variation in the type of cell differentiation in various regions.

TOXEMIA

The physical condition of the patient may have an important bearing on the reaction produced by the radiotherapy. Many of these patients are anemic and cachectic, and suffering from toxemia as a result of the absorption of necrotic carcinomatous tissue. Frequently, they are septic due to a local infection of the ulcerated areas. The immediate result of the radiotherapy in such cases is to produce a severe reaction on account of the absorption of the autolytic and toxic protein substances which have been liberated by the destruction of the cancer cells.

This "radiation sickness" is naturally more severe in those patients who are already toxic and anemic, and this systemic condition prevents the defense mechanism from promoting the prompt healing of tissues. The effect of the radium is to produce a leucopenia, and the patient's

resistance needs to be fortified to combat this condition. Hence, the value of blood transfusions is to enable the patient to "weather the storm" and make a smoother recovery.

External Radiation.—As the beneficial action of the gamma rays of radium is limited to a range of 3 to 4 cm., it is apparent that if the cancer has spread beyond this distance, the local radium application will not be sufficient to eliminate the disease. Bonney found 43 per cent of gland involvement in his operative cases, and it is to this that he attributes the superiority of surgery.

External radiotherapy, by means of the high voltage deep x-ray apparatus, or by using a radium pack, or "bomb" at a distance, is necessary to attack the disease when beyond the reach of the internal radiation. The use of radium at a distance requires a large amount of radium, 2 to 4 Gm., so that the method is not available except in a few institutions.

Nearly all radiologists are of the opinion that the combined treatment is necessary to obtain the greatest benefit.

The Limitations of Radiotherapy.—To find the balance between the dosage necessary to destroy completely the neoplastic cells, and at the same time keep within the minimum dosage which will destroy normal tissues, is the problem that the radiologist must meet. It is obvious that the conditions in each case may vary greatly. The type of cell, the physical characteristics of the growth, the size and condition of the organs affected, and the constitutional state of the patient are all factors which must be carefully weighed in planning the dosage and technique best suited for the case under consideration.

Regaud has pointed out that radium is not a cure for every case of cancer. It is with the epidermoid type that the best results have been obtained. The adenocarcinomatous group are more difficult to cure. In the cases where the parametria are involved, the proportion of five-year cures is small, although the palliative results, even in many advanced cases, are of great value in prolonging life and reducing suffering.

THE COMPLICATIONS OF RADIOTHERAPY

There is a general impression that the convalescent period with radium is without the same suffering and is much shorter than with surgery. This impression, however, is open to question, and a careful comparative study of postirradiation convalescence with convalescence from radical surgery should be made to evaluate properly radiotherapy. In other words, "What price radium?"

After an experience of more than fifteen years in the use of radium in carcinoma of the uterus, we believe that a ten-year postirradiation observation period gives us a more accurate evaluation of the curability of cancer by radiation than the usual five-year standard. An estimation of postirradiation mortality and morbidity is naturally confused and complicated by the ravages of the disease itself.

As three-fourths of all cases seen do not survive the five-year period, it is reasonable to assume that the cancer is responsible for the mortality and much of the morbidity rather than the irradiation.

An approximate indication of the incidence of complications in a series of 688 cancer cases treated with radium, seen during three five-year periods, shows that pyometra was observed in 7.9 per cent, peritonitis and sepsis in 1.5 per cent, intestinal obstruction in 3.6 per cent, patients

developing fistulas in 8.7 per cent, severe hemorrhage in 12.9 per cent, rectal disorders in 6.1 per cent, bladder and urethral symptoms in 9.8 per cent, the upper urinary tract was involved in 5.6 per cent, upper gastrointestinal symptoms in 2 per cent, blood and lymphatic obstruction in 4.2 per cent, and nervous disorders, pain, etc., in 3.7 per cent.

Upper urinary tract disease, which occurred in 39 of the 688 cases, was usually a late development and was due generally to obstruction of the ureter, with resulting infection, hydronephrosis and pyonephrosis, or destruction of the kidney. The ureteral obstruction was demonstrated by catheterization in these cases and was usually 4 cm. from the orifice. The action of radium, which produces a proliferation of the connective tissues with subsequent contraction, is responsible for the complication in many cases, due to the proximity of the ureters to the sides of the cervix as they pass through the base of the broad ligaments, although the invasion of the carcinoma into the same region is a frequent cause. Therefore, all patients should have a complete urologic examination before being given radiation therapy in order to evaluate properly damage by radium.

In the earlier cases, hopeless cases, and cases lost in the follow-up examinations, complications were not always accurately recorded. There are also many duplications, as one complication precedes or is an early stage of another. This gives us an index of the price these patients had to pay for radium therapy. Except for hemorrhage, each of these complications occurred in less than 10 per cent of the cases. The majority of complications are less frequent in the patients destined to survive, and many are of a transitory nature.

All of the untreated patients die of the disease, and the complications of the various organs involved are, of course, due to the carcinoma. In the treated patients that die the complications often appear shortly before death, and in many they are also due to the disease itself and not to the radiotherapy. The development of complications, then, we must always regard as an unfavorable sign, as in many cases it is an indication of a probable extension of the carcinoma. However, we have been agreeably surprised in some instances to see a patient whom we had considered in a hopeless condition report to the follow-up clinic some months later restored to health, with an arrest of the disease. These patients undoubtedly were suffering from late radium reactions and not from the progress of the carcinoma. We have learned, therefore, to reserve judgment on the outcome of these hopeless cases.

The essential features of the technique employed at the Woman's Hospital in carcinoma of the cervix are as follows:

The classification of the extent of the disease by both the Schmitz and the League of Nations systems, and the recording of the same on life-sized charts.

The preliminary building-up of the patient's resistance in cachectic cases by a blood transfusion.

Anesthesia of some type is necessary for accurate diagnosis and biopsy, and for the correct application of the radium.

A biopsy is taken with the radio-knife.

An initial dosage of 3,600 to 4,200 mg. hours of radium is given, depending upon the extent and size of the cancerous growth. One hundred milligrams are placed intracervically, with the equivalent of 1 mm. of platinum screening, and in the periphery at the junction of the cervix with the vaginal fornices 4 or 6 platinum needles (0.5 mm.), containing 12½ to 13 mg. each, are inserted for twenty-four hours. Ten to twelve days later a second application of 75 mg. of radium in 6

platinum needles in two silver boxes in a spring colpostat is made to the vaginal vault. Each box approximates the lateral fornices of the vagina at the base of the broad ligaments for twenty-four hours. Thus the total radium therapy averages from 5,400 to 6,000 mg. hours.

In cases where there is an exuberant cauliflower mass protruding into the vagina, it is removed with the high frequency knife before applying the radium.

We stress the importance of distance screening by distending the vagina with gauze to its capacity to keep the bladder and rectum as far away as possible from the radium rays, and we use a self-retaining catheter to keep the bladder collapsed during the radium application. We believe that anchoring the radium tube in the uterus is an important detail.

Potassium permanganate douches and an elevated posture to promote drainage and separation of any slough are begun at once.

Adjuvant high-voltage roentgen therapy has been employed since 1930, and since 1933, the fractional method of Coutard has been used whenever it is possible to have continued cooperation of the patient for the necessary length of time. In certain cases of advanced carcinoma, we precede the application of radium with roentgen therapy, according to Healy's plan. Two hundred roentgen units are given to one anterior and one posterior portal daily until all portals have received 2,000 to 2,400 roentgen units each.

The outstanding feature of our method, however, is the frequent follow-up inspection made by the surgeon himself throughout the five-year period, if at all possible. During the first three years a monthly inspection is made, and after that the patient is seen every two or three months. If the follow-up examination discloses evidence of a beginning recurrence in the vaginal walls or fornices, a further irradiation is given in time to check the recurrence in its incipiency.

In carcinoma of the fundus uteri, we believe that panhysterectomy should be resorted to wherever possible and that the ideal procedure is the combined method of diagnostic curettage with immediate insertion of radium in the cavity, the radium to remain for from 2,400 to 3,600 mg. hours, followed by a panhysterectomy and salpingo-oophorectomy within four to six weeks, and on recovery a course of roentgen therapy, preferably by the Coutard technique.

RESULTS

The comparison of statistical results in the treatment by radiotherapy of carcinoma of the cervix in the different clinics of the world shows an improvement over the earlier reports. The report published by the League of Nations in 1938 shows the results of the 1931 series from seven clinics in Europe, and two from the United States, the Memorial and the Woman's Hospital clinics representing this country. A total of 5,672 patients were treated, with a relative 5-year cure rate of 26.3 per cent, and of the 607 Stage I cases, the relative cure rate was 55.2 per cent.

A survey of the six statistical reports of our results shows an improvement in the relative five-year cure rates we have obtained as follows: 1925, 23.6 per cent; 1928, 23.1 per cent; 1930, 25.5 per cent; 1932, 24.8 per cent; 1934, 25.28 per cent, and 1937, 28.5 per cent.

CONCLUSIONS

The safe and efficient use of radium requires judgment and experience.

A thorough understanding of its action and an appreciation of the complexities of its application are necessary, otherwise a grave re-

sponsibility is assumed in not giving the patient the full benefit of our present-day knowledge.

Radium is a two-edged weapon, and a proper training in its use is just as essential as in surgery.

It is well to emphasize the fact that the safe employment of radium requires experienced piloting, as we are sailing in tortuous channels with rocks on either side. It may be likened to Vergil's lines:

> "There on the right her dogs foul Scylla hides,
> Charybdis roaring on the left presides."

101 East 80th Street

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MARCH 12, 1940

The following papers were presented:

Endometrium-Like Mucosa Lining the Fallopian Tube. Dr. Andrew A. Marchetti. (By invitation.) (For original article, see page 69.)

Management of the Occipitoposterior and Retraction Ring Dystocias in Primiparas. Dr. George G. Cochran, Jr. (By invitation.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF FEBRUARY 1, 1940

The following paper was presented:

Toxemias of Pregnancy. Dr. M. Pierce Rucker, Richmond, Va. (By invitation.)

MEETING OF MARCH 7, 1940

The following papers and case reports were presented:

The Suppression of Lactation by Stilbestrol. Dr. C. W. Mucklé. (For original article, see page 133.)

Stilbestrol in the Treatment of Menopausal Symptoms. Drs. F. L. Payne and C. W. Mucklé. (For original article, see page 135.)

Chronic Nephritis and Pregnancy Fatalities in Philadelphia. Dr. N. F. Paxson.

Successive, Coexistent Tubal Pregnancies. Drs. C. A. Behney and W. J. Hanes. (For original article, see page 155.)

Removal of a Graefenburg Ring Without Interruption of Pregnancy. Drs. R. A. Kimbrough and P. Tompkins. (For original article, see page 156.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 16, 1940

The following papers were presented:

The Treatment of Oliguria and Anuria. Drs. W. J. Dieckmann and S. Kramer. (For original article, see page 61.)

Congenital Goiter. Drs. A. H. Parmelee, Edward Allen, Irving F. Stein, and Henry Buxbaum. (For original article, see page 145.)

Epidemic Infectious Diarrhea of the Newborn Infant. Drs. R. S. Cron, H. W. Shutter, and A. H. Lahmann. (For original article, see page 88.)

MEETING OF MARCH 15, 1940

The following papers were presented:

A Study of 1200 Cases of Hysterectomy. Dr. Philip H. Smith. (For original article, see page 118.)

Prolapse of the Umbilical Cord. Drs. W. F. Mengert and F. H. Longwell. (For original article, see page 79.)

An Acute Crisis of Suprarenal Insufficiency Complicating Pregnancy. Drs. C. E. Galloway, D. C. Sutton and John Ashworth. (For original article, see page 148.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 2, 1940

The following papers were presented:

Syphilis and Pregnancy. Dr. William T. Daily.

Chorioepithelioma. Dr. C. W. Mueller, H. J. Greene and J. Klein.

Uterine Bleeding in the Last Trimester of Pregnancy. Dr. J. T. Wallace. (For original article, see page 128.)

Renal Insufficiency Following Transfusion of Compatible Blood. Dr. H. H. Brainard. (For original article, see page 142.)

MEETING OF MARCH 1, 1940

The following paper was presented:

Relationship of the Thyroid and Adrenal Glands to the Toxemias of Pregnancy. Dr. E. C. Hughes, Syracuse, N. Y. (By invitation.) (For original article, see page 48.)

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 5, 1940

The following papers were presented:

Four Unusual Cases of Ectopic Pregnancy. Dr. David B. Ludwig.

The Misleading History in Four Cases of Ectopic Pregnancy. Dr. S. A. Rubin.

Ovarian Cysts Complicating Pregnancy. Dr. R. Charles Nucci.

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF FEBRUARY 20, 1940

The following paper was presented:

Surgical Complications of Pregnancy. Drs. J. A. Smith and M. K. Bartlett.

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

MEETING OF FEBRUARY 9 AND 10, 1940

The following papers were presented:

Use of Radium in the Menopausal Type of Uterine Hemorrhage. Dr. G. R. Holden.

The Third Stage of Labor With a Description of a New Method of Expression of the Placenta. Dr. C. J. Andrews.

The Post-Partum Bladder. Dr. J. R. Perdue.

Indictment of Diethylstilbestrol. Drs. R. B. Greenblatt, R. Torpin and W. R. Brown.

Nutrition Study in Pregnancy. Dr. Philip F. Williams, Bernard Hark, and Florence G. Fralin. (For original article, see page 1.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Myoma and Endometrioma

DaCosta, C. C.: Myoma of the Vagina, Rev. de gynec. e d'Obst. **1**: 257, 1939.

The author states that myoma of the vagina is very rare. He was able to find only one case in the literature, reported by Caper in 1935. The article deals with the differential diagnosis between cysts and tumors of the Bartholin gland, and the author describes in detail a case of myoma of the vagina, operated on by him. Histologic examination reveals all the characteristics of a myoma. The article closes with several theories on the etiology of vaginal myoma and its prognosis.

MARIO A. CASTALLO

Kanter, A. E., and Klawans, A. H.: Fibroids of the Uterus, Illinois M. J. **76**: 459, 1939.

The authors have drawn their conclusions from 300 consecutive patients operated upon at the Cook County Hospital. They find that parity has no demonstrable relation to fibroids, although sterility may be a direct result of the tumor. They also find that the textbook symptoms ascribed to fibroids of the uterus, namely, menorrhagia, dysmenorrhea, leucorrhea, and bladder symptoms, are determined entirely by the location of the growth and not due to the fibroid per se. In conclusion, the authors make a plea against additional elective surgery, such as appendectomy or perineorrhaphy, in conjunction with hysterectomy, as these elective procedures apparently doubled the mortality figures in their series of cases.

EUGENE S. AUER

Portes, L.: Note on the Connection Between Uterine Fibromas and Hyperfolliculinemia, Bull. Soc. d'obst. et de gynéc. **27**: 275, 1938.

The author reports a case in which he found an excessive amount of estrin in the blood, coincident with rapid growth of a fibroid uterus. This finding supports the contention of Seitz, Moench, and Witherspoon that uterine fibroids are associated with an increase in amount of circulating estrin. The arguments in favor of this theory are as follows: (1) Uterine fibroids appear only after puberty and disappear after the menopause, and this agrees with the period of estrin activity of the ovary. (2) The suppression of ovarian estrogenic activity by radiation results in the diminution or disappearance of fibroids. (3) Uterine fibroids sometimes grow rapidly during pregnancy, at which time there is a very important increase in the amount of circulating estrin. Hence, it should be possible to treat fibroids with endocrines at least at the beginning of their growth and reserve operation for mechanical complications of the tumor or for tumors which undergo degeneration.

J. P. GREENHILL

Langlois: A New Treatment of Uterine Fibroids, Bull. Soc. d'obst. et de gynéc. **27**: 179, 1938.

In the treatment of uterine fibroids, Langlois has been using halogen salts of magnesium. Hypodermic injections are administered every day for four to six months. Then the treatment is stopped for one or two months and again resumed. Improvement is noticed after the first course of treatment. The author reports four cases where the bloody discharge disappeared and the fibroid masses slowly regressed.

J. P. GREENHILL

Kangas, Toivo: Submucous Myomas, Expecially with Regard to Their Operative Treatment, Ann. Inst. Obst. et Gynec. Universitatis **11:** 89, 1939.

The author collected the cases of submucous myoma treated at the Women's University Clinic in Helsinki and at Engstrom's Clinic. Of the 383 cases, 164 were pedunculated myomas: 96 were expelled into the vagina, 51 into the cervical canal and 17 remained in the uterine cavity. The submucous type of myomas seemed to be comparatively frequent in multiparas and particularly during the last decade of the procreative age. Ten per cent of the submucous myomas evoked pathologic hemorrhages. Of the myomas expelled into the vagina 75 per cent caused metrorrhagial hemorrhages in 75 per cent of the cases. Treatment by rest in bed and opium stopped pain. Before operation, an attempt should be made to increase the hemoglobin to above 50 per cent. The conservative extirpation of submucous myomas with a thin pedicle is a fairly harmless interference. The mortality was 0 in 113 cases. In primary radical operations, there is always the danger of complications (parametritis, thrombophlebitis, etc.).

J. P. GREENHILL

Vanverts, J.: All Uterine Fibroids Need Not Be Operated Upon Routinely, Gynécologie **37:** 385, 1938.

Contrary to many surgeons, the author believes that frequently uterine fibroids remain latent and permit their hosts to lead a perfectly normal life. The number of such tumors is not small. Since there is some danger in operating or in using radiation therapy, treatment should be advised only when serious accidents or disturbances arise which must be suppressed. Sometimes medical measures may be used to overcome the inconveniences of fibroids.

In cases where active treatment is deferred, the fibroids must be examined systematically, at least every six months. The patient must also be warned to notify her physician should any disturbance arise. Such routine examination should not cease at the menopause, because fibroids may grow or produce trouble after the change of life.

J. P. GREENHILL

Azevedo, Moura, and Dutra, Licinio H.: High Partial Hysterectomy for Uterine Fibroma, Rev. de obstet. e ginec. de São Paulo **4:** 3, 1939.

The authors present a new technique utilizing a U incision for partial hysterectomy in uterine fibroma. The incision is made in such a manner as to remove the mid-portion of the uterus, leaving the adnexa on both sides attached to the uterus. The author then utilizes the remaining sides of what formerly was the uterine body to cover the defect made. The remaining portions of the uterus are united from side to side.

MARIO A. CASTALLO

Dougal, Daniel: Endometriosis as a Pathological and Clinical Problem, Edinburgh M. J. **45:** 61, 1938.

For every 100 cases of uterine fibroids, there are 6 cases of internal and 25 cases of external endometriosis. The latter is met with as the principal lesion or as an important complication in about 10 per cent of all abdominal operations performed on the female genital organs.

The influence of endometriosis on the patient's general health depends on the frequency and severity of the principal symptoms and on the extent of the surgical treatment necessary to deal with them.

Pain in the lower abdomen is an important symptom of both internal and external endometriosis and may occasionally be of great severity. Dysmenorrhea, however, is undoubtedly the most characteristic symptom, particularly if of recent origin or becoming increasingly severe, although it was present in only about 50 per cent of the author's cases.

Menorrhagia and epimenorrhagia are present in about 40 per cent of the cases and may be extremely severe, especially if the uterus is involved. The excessive or irregular blood loss may be partly due to the presence of associated fibroids, but is mainly a reflection of disturbed ovarian function; indeed in some cases the uterine endometrium has the thick, polypoid and hyperplastic appearance characteristic of metropathia hemorrhagica.

Dyspareunia may cause the patient much discomfort and mental distress and is met with in its most severe form when the endometriosis involves the structures behind the posterior vaginal fornix.

On the other hand, severe pelvic endometriosis may be quite painless, but this is exceptional, and the pain, particularly during menstruation, is frequently so severe that the patient is willing to undergo any treatment, however radical, to obtain relief from it.

Endometriosis has an adverse influence on fertility, and in this connection it is important to consider the age incidence of the disease.

Excluding cases with associated fibroids, single women and women married less than three years, 40 per cent of the patients were sterile, 32 per cent had not been pregnant for at least ten years and 23 per cent for at least five years.

Finally there is the question of treatment. When the lesions are extensive this must be radical and either surgical or radiologic. The author's preference is for surgery, and in severe cases he generally performs a hysterectomy with removal of both appendages. It is unnecessary and in fact dangerous to dissect out growths from the bowel wall, as there is ample evidence that these will retrogress if both ovaries are removed.

In less severe cases, particularly in young women, treatment should if possible be conservative, but it must be realized that this may afford only temporary relief and have to be followed later by more radical measures.

It is unfortunate that so many radical operations appear to be necessary, but one must remember that to be truly successful, conservative treatment should not only conserve function but also cure the patient. Many keen advocates of conservative surgery are likely to forget this in their anxiety to preserve the reproductive function.

In the meantime it should be possible to reduce the incidence of external endometriosis by creating such conditions as subinvolution, backward displacements of the uterus, and uterine fibroids which may predispose to retrograde menstruation, and by carrying out certain intrauterine diagnostic and operative procedures at a time and in a manner least likely to drive fragments of endometrium into and through the Fallopian tubes.

J. P. GREENHILL

Heynemann, T.: Endometriosis, Zentralbl. f. Gynäk. 63: 1, 1939.

The diagnosis of Endometrioma is still difficult. The condition can be recognized easily if it is visible through a speculum, colposcope, or proctoscope. In cases of ovarian endometriosis, pelvic puncture may help if the findings are in agreement with the clinical symptoms. In cases of endometriosis of the rectovaginal septum, biopsy may be useful. Philipp mentioned that the administration of large doses of estrin and progestin increases the size and sensitivity of endometrial masses.

The author followed up the patients who had been treated for endometriosis in his clinic from 1920 to 1937. Of 40 women operated upon for ovarian endometriosis, one died as a result of the operation. In 21 of the remaining 39 women, some healthy-looking ovarian tissue was left behind, in 15 of them a whole ovary, and in the other 6 only a piece of ovary. In not one of these 21 women was there a recurrence of the endometriosis. In 13 women the menstrual function was maintained but only one became pregnant. The frequency of sterility in cases of endometriosis is well known, even when the tubes are patent.

In 47 women tubal adenomyosis in the form of a salpingitis isthmica nodosa was found. In 11 of these (22 per cent) tubal pregnancies were encountered. One of these 47 women died of pulmonary embolism.

In cases of endometriosis where operation is contraindicated, roentgen ray therapy should be carried out. This will check bleeding and dysmenorrhea. During operation for endometriosis, healthy ovarian tissue should not be removed, especially if the tubes are patent. In cases of retrocervical endometriosis, the cervix should be removed but not the involved portion of intestine.

Not all cases of endometriosis require treatment. Only those which grow and produce symptoms should be treated. It has been shown that definitely proved endometriosis may not grow during a period of many years, even if ovarian tissue is left behind. This may occur even if one or both entire ovaries are left.

J. P. GREENHILL

Henderson, D. N.: Pelvic Endometriosis, Canad. M. A. J. **40**: 34, 1939.

Forty cases of pelvic endometriosis are reviewed. The chief symptoms were abdominal pain in 30; menorrhagia or metrorrhagia in 22; and dysmenorrhea in 9. Fibroid tumors of the uterus were present in 15 instances. The rectum and sigmoid were involved either by direct invasion of endometrial adenomas or by adhesions in 23 patients. The danger of mistaking such endometrial invasion for carcinoma of the bowel is pointed out.

Treatment of pelvic endometriosis is surgical and depends on the extent of the disease. Bilateral salpingo-oophorectomy and hysterectomy was the operation performed in 32 of the 40 cases.

CARL P. HUBER

Holtz, F.: Endometrioma With Pregnancy Reaction, Gynéc. et obst. **38**: 278, 1939.

In endometriomas removed during various phases of the menstrual cycle, histologic study has revealed corresponding periodic changes. One would expect these transplants to assume characteristic features when they occur coincidentally with pregnancy.

Four years following the removal of the right ovary which contained a hemorrhagic cyst, probably an endometrioma, a 37-year-old primipara suffered from metrorrhagia. For relief, curettage was performed twice. She was examined nine years after the right salpingo-oophorectomy, following a two month's period of amenorrhea, and the uterus was found to be definitely enlarged and softened. In the posterior vaginal fornix, there was found a walnut-sized tumor, having the typical appearance of an endometrioma. A small portion was biopsied, and histologic examination revealed glands lined with cuboidal, epithelial cells in the secretory phase surrounded by connective tissue, having a decidual reaction. The Aschheim-Zondek test was positive, and seven months later the patient was delivered at term.

These findings demonstrate the fact that endometriomas in association with pregnancy undergo changes that correspond with those in the uterine mucosa.

ARNOLD GOLDBERGER

Hobbs, John E., and Bortnick, A. R.: Endometriosis of the Lungs, Surg. Gynec. Obst. **69**; 577, 1939.

Clinical and pathologic observation, information gleaned from the literature, and a study of a series of experiments cause one to believe that endometrial tissue is transported through lymphatics and veins, and that autotransplanted uterine mucosa of the rabbit will grow in the lung tissue.

A plausible explanation for vicarious menstruation is evident, since endometrial tissue can get into the general circulation either through a patent foramen ovale or by propagation through the pulmonary circulation.

Aberrant endometrial tissue has characteristics which would indicate it has increased potentiality to become malignant.

WM. C. HENSKE.

Navratil, E.: Endometriosis of the Extremities, Klin. Wchnschr. 18: 905, 1939.

In 1936, the author had reported the first known incident of endometriosis in the muscles of the arm in a 25-year-old patient. The tumor was a date-sized fibrotic mass in the carpi radialis externi muscle. Histologic examination showed a typical endometriosis with chronic inflammatory reaction. Repeated gynecologic examinations during 1935 and 1936 revealed no evidence of adenomyosis uteri nor of intra-abdominal endometriosis. Her past history was likewise negative.

Since this first report, the patient had a definite increase in the duration of her menstrual periods with marked increase in blood loss and the development of protracted dysmenorrhea. Her menstrual period also changed from a regular 28-day cycle to one that varied between 28 and 36 days.

Since November, 1938, the patient complained of continued pain in the right lower quadrant and moderate fever. Examination of the arm at this time revealed no recurrence of the endometriosis. The patient was operated upon in December, 1938. Both ovaries showed cystic degeneration and a total hysterectomy, bilateral ovarian resection and appendectomy were done. Careful search of the peritoneal cavity revealed no evidence of intra-abdominal endometriosis. Histologic examination of the uterus showed typical adenomyosis uteri interna with marked invasion of the myometrium by endometrial glands. The resected portions of both ovaries and of the appendix showed no endometriosis.

Here then is a patient in whom endometriosis of the muscles of the arm developed three years before any evidence of adenomyosis of the uterus could be elicited. The author is of the opinion that the onset in all probability dates back to a therapeutic abortion which had been previously performed. The author concludes that such metastasis must occur by way of the blood stream, the transmission being similar to that of living decidual cells during pregnancy. It would seem impossible to trace endometriosis as here described through any form of lymphatic transmission.

RALPH A. REIS

Item

American Board of Obstetrics and Gynecology, Inc.

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 4, 1941, at 2:00 P.M. Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 5, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Cleveland, Ohio, immediately prior to the 1941 meeting of the American Medical Association.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pennsylvania.

Candidates certified by the American Board of Obstetrics and Gynecology at the June, 1940, examinations held at Atlantic City, N. J.

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KENNETH M. ARCHIBOLD, Albany, N. Y.
IRVING H. BECKWITH, White Plains, N. Y.
KARL M. BEIERLEIN, Fort Wayne, Ind.
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SAMUEL G. BERKOW, Perth Amboy, N. J.
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JOHN N. BORBONUS, Johnstown, Pa.
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WILLIS E. BROWN, Ann Arbor, Mich.
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LAWRENCE R. WHARTON, Baltimore, Md.
JOSEPH R. WHERRITT, Salt Lake City, Utah
HAROLD M. WILEY, Cincinnati, Ohio.
RICHARD J. WILLIAMS, Lynn, Mass.
WILLIAM M. WILSON, Portland, Ore.
ARTHUR C. WOGGON, Rochester, N. Y.
CHARLES B. WOODMAN, Morristown, N. J.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* E. J. Litzenberg. *Secretary,* Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June, 1941, Colorado Springs, Colo.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* James R. McCord. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.

Central Association of Obstetricians and Gynecologists. *President,* Jennings C. Litzenberg, Minneapolis, Minn. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.

South Atlantic Association of Obstetricians and Gynecologists. *President,* M. P. Rucker, Richmond, Va. *Secretary,* Robert A. Ross, Durham, N. C. Next meeting, February 7 and 8, 1941, Jacksonville, Fla.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Norman F. Miller, Ann Arbor, Mich. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1941, Cleveland, Ohio.

New York Obstetrical Society. *President,* Thomas C. Peightal. *Secretary,* Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* Roy W. Mohler. *Secretary,* John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Harold K. Gibson. *Secretary,* James A. Gough, 104 S. Michigan Ave., Chicago, Ill., Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* Frances Doyle. *Secretary,* John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue.

Baltimore Obstetrical and Gynecological Society. *President,* N. J. Eastman. *Secretary,* Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* E. W. Enz. *Secretary,* Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Esther C. Wallner. *Secretary,* Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* S. A. Chalfant. *Secretary,* Dr. Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, April, and June.

Obstetrical Society of Boston. *President,* Raymond S. Titus. *Secretary,* Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

New England Obstetrical and Gynecological Society. *President,* Thomas Almy. *Secretary,* R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.

Pacific Coast Obstetrical and Gynecological Society. *President,* Alice F. Maxwell. *President-Elect,* John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast. Next meeting, San Francisco, Calif., Nov. 6 to 9, 1940.

Washington Gynecological Society. *President,* H. P. Ramsey. *Secretary,* James R. Costello, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* H. C. McGee. *Secretary,* H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* Percy H. Swahlen. *Secretary,* Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Floyd Bell. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. *President,* H. Reid Robinson, Galveston, Texas. *Secretary-Treasurer,* J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Marlin, Texas, October, 1940.

Books Received

FUNDAMENTALS OF INTERNAL MEDICINE. By Wallace Mason Yater, professor of medicine and director of the department of medicine, Georgetown University School of Medicine, etc. First edition—revised. 1021 pages with 254 illustrations. D. Appleton-Century Company, New York, 1940.

SYNOPSIS OF SURGERY. By H. E. Mobley, M.D., F.A.C.S., chief of surgery at St. Anthony Hospital, Morrilton, Arkansas. 375 pages with 339 text illustrations including 39 in color. The C. V. Mosby Co., St. Louis, 1940.

SYNOPSIS OF OBSTETRICS. By Jennings C. Litzenberg, professor emeritus of obstetrics and gynecology, University of Minnesota Medical School, Minneapolis. 394 pages with 157 illustrations including 5 in color. The C. V. Mosby Co., St. Louis, 1940.

CYCLOPROPANE ANESTHESIA. By Benjamin Howard Robbins, associate professor of pharmacology, Vanderbilt University School of Medicine. 175 pages, illustrated. Williams & Wilkins Company, Baltimore, 1940.

CONGENITAL MALFORMATIONS. By Douglas P. Murphy, assistant professor of obstetrics and research associate in the Gynecean Hospital Institute of Gynecologic Research, University of Pennsylvania. University of Pennsylvania Press, Philadelphia, 1940.

SPECIALTIES IN MEDICAL PRACTICE. Edited by Edgar van Nuys, chief of a section in the division of medicine, The Mayo Clinic, Rochester, Minn. etc., with a Foreword by Donald C. Balfour, consultant in surgery, The Mayo Clinic. Loose-Leaf, in two volumes, illustrated. Thomas Nelson and Sons, New York, 1940.

BIOLOGICAL SYMPOSIA. Edited by Jaques Cattell, editor of The American Naturalist and American Men of Science. 238 pages, illustrated. The Jaques Cattell Press, Lancaster, Pa., 1940.